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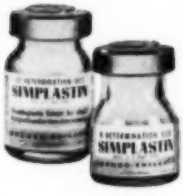

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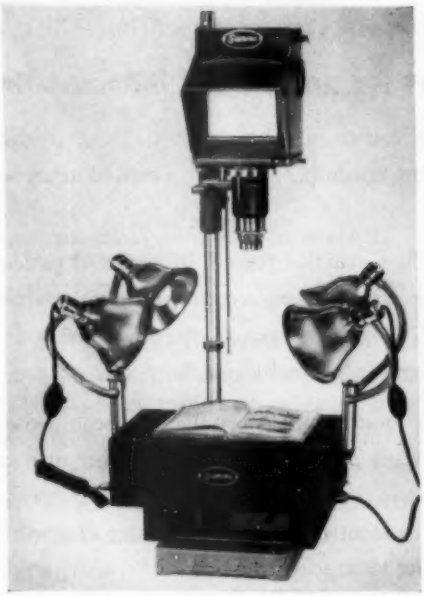

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VOLUME 58 AUGUST 1954 NUMBER 2

UNUSUAL CARCINOMAS OF THE PANCREAS

SHELDON C. SOMMERS, M.D.
AND
WILLIAM A. MEISSNER, M.D.
BOSTON

THE GREAT majority of carcinomas of the pancreas fall into a rather uniform variety of growth patterns that are variously described as adenocarcinoma, carcinoma simplex, or undifferentiated carcinoma.* However, a review of the pathology of 142 autopsied cases of pancreatic carcinomas † revealed 15 cases with

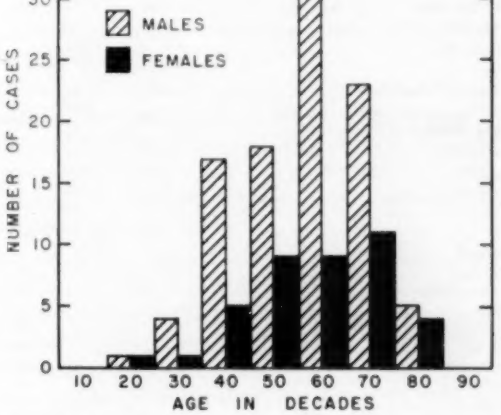


Fig. 1.—Ages by decades in 142 autopsied cases of pancreatic carcinoma.

unusual growth patterns, not only differing from the conventional, but also remarkable because of the surprising diversity of types. Inasmuch as such unusual tumors

This investigation was aided in part by research grants C-1413 and C-1754 from the National Cancer Institute of the National Institutes of Health, United States Public Health Service.

From the Departments of Pathology, New England Deaconess Hospital, Harvard Cancer Commission, and Massachusetts Memorial Hospitals, Boston, and Pondville Hospital (Massachusetts Department of Public Health), Walpole, Mass.

* References 1 through 5.

† From the files of the New England Deaconess Hospital, Peter Bent Brigham Hospital, and Pondville State Hospital. Dr. Samuel P. Hicks, formerly Pathologist, Peter Bent Brigham Hospital, allowed access to cases there.

in the pancreas seem to be less well appreciated and understood than conventional pancreatic carcinomas, a description and discussion of the individual patterns seemed warranted.

Of the total 142 cases of pancreatic carcinoma reviewed, 101 were in men and 41 in women. The age range was from 23 to 86 years, with peak incidence in both

TABLE 1.—*Pathologic Features of 127 Conventional Pancreatic Carcinomas*

	Adenocarcinoma (84)	Carcinoma Simplex (43)
Origin		
Ducts	53	16
Acini	8	7
Ducts and acini	6	3
Ducts and islets	3	4
Islets	3	4
Ducts, acini, islets	..	1
Indeterminate	11	8
Site		
Undetermined	4	1
Head	46	20
Body	4	2
Head and body	3	2
Tail	9	6
Body and tail	4	..
Head, body, tail	8	9
Size range, cm.	0.7 to 13	1 to 18
Invasion		
Perineural lymphatics	41	24
Ducts	16	5
Blood vessels	13	11
Stroma scirrhous	24	10
Secretion		
Mucinous	20	11
Serous	11	3
Both	4	1
Metastases *		
Liver	80	
Lymph nodes	71	
Lungs	49	
Gastrointestinal tract	19	
Adrenal	17	
Peritoneum	14	
Diaphragm	10	
Spleen	9	
Bone marrow	9	
Kidney	7	
Pleura	7	
Thyroid	5	
Gall bladder	4	
Heart	4	
Brain	4	
Bladder	4	
Ovary	3	
Subcutaneous tissue	3	

* Also one each of the epididymis, nerve, parathyroid, prostate, testis, ureter, and uterus.

sexes at between 60 and 70 years of age (Fig. 1). In Table 1, the features of the 127 pancreatic carcinomas with conventional growth patterns are given. Distinctions between adenocarcinoma and carcinoma simplex are chiefly those corresponding to the higher grade of malignancy of the latter. One functioning [6] and six apparently

nonfunctioning islet cell adenocarcinomas observed are included in the tabulation.‡ Other neoplasms developed from ducts, from acini,§ from both ducts and acini, or from all three pancreatic epithelial components.[11]

The 15 unusual carcinomas in question could be classified into five general growth patterns: Pleomorphic carcinoma, cystadenocarcinoma, papillary adenocarcinoma, adenoacanthoma, and ciliated adenocarcinoma. Their characteristics will be described in this order.

GENERAL GROWTH PATTERNS

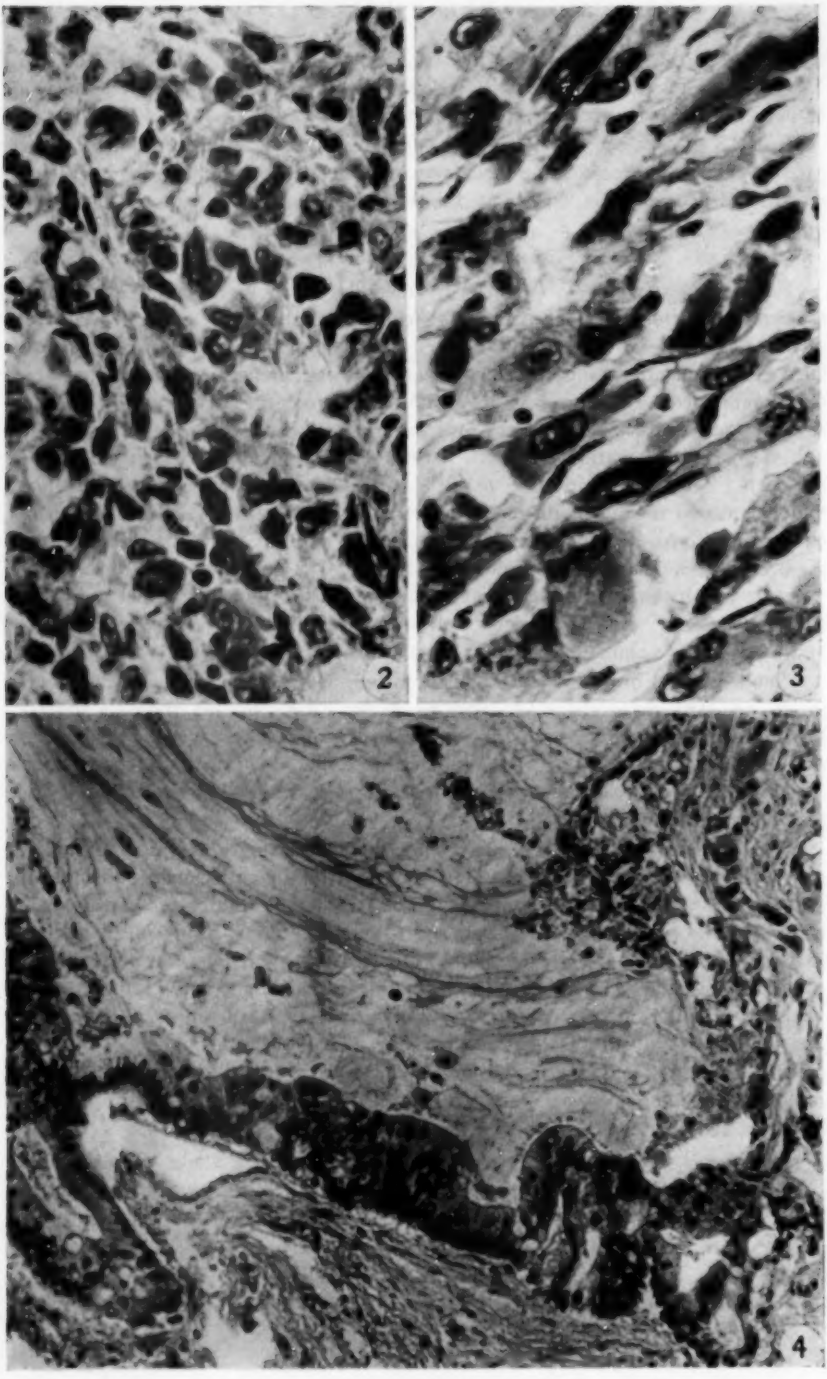
Pleomorphic Carcinoma (giant cell,[12] medullary,[13] or sarcomatoid carcinoma ‖; carcinosarcoma [15]).—Salient pathologic features of the three cases observed are included in Table 2. Grossly the tumors were not distinguishable from the usual hard gray-white appearance of ordinary pancreatic carcinomas, except for one, which was surrounded by a large mass of hemorrhagic necrosis. Histologically the pleomorphic carcinoma is probably the most bizarre carcinoma of the pancreas and has one of the most remarkable growth patterns of any neoplasm. Even pathologists experienced in the classification of neoplasms, when confronted with this tumor, may be misled into such diagnoses as rhabdomyosarcoma, malignant melanoma, chorioepithelioma, hepatoma, or angiosarcoma. In many respects the resemblance to giant cell carcinoma of the thyroid was striking. The cells were multiform and of large size, with abundant granular and vacuolated eosinophilic cytoplasm and greatly enlarged nuclei. Tumor giant cells with large eosinophilic nucleoli were numerous and mitoses quite abundant (Fig. 2).

There was no organoid pattern, but, rather, a grotesque tangle of tumor cells intermixed with hemorrhage and necrosis. When closely packed, the cells appeared sarcomatous (Fig. 3). Examination at autopsy, however, showed in the pancreas areas of readily recognizable, moderately well-differentiated primary adenocarcinoma shading off peripherally into the wild pleomorphic carcinoma which also characterized the metastases (Fig. 4).

The original case, which focused attention on pleomorphic carcinoma of the pancreas, was found in a 48-year-old man, who was operated upon twice. At the first operation, a cystic pancreatic tumor was removed. Microscopically, this malignant cystadenoma had a fibrous wall and a lining of mucus-producing epithelium, partly growing as adenocarcinoma (Fig. 5). In a few areas, pleomorphic cells with lymphatic invasion were found in the stroma of the cystic portions (Fig. 6). At the second operation, four months later, a mass in the abdominal wall was found which was composed microscopically of the pure pleomorphic carcinoma (Fig. 7). The patient died two months later. An autopsy was not performed. Since this report was completed, another autopsied case has been observed in a man 39 years old, with metastases from the tail of the pancreas to lymph nodes and liver.

Cystadenocarcinoma.—Malignant changes in pancreatic cystadenomas have been much discussed ¶ but are infrequent. Less than 20 genuine cystadenocarcinomas have been reported.[19] Two examples were found in this series, the tumors being grossly cystic and containing internal papillary or irregularly thickened areas. The

‡ References 7 and 8.
§ References 9 and 10.
‖ References 5 and 14.
¶ References 16 through 19.



Figures 2-3-4

(See legends on opposite page)

cyst in the head of the pancreas was 1 cm. in diameter and that in the tail was 5 cm. Microscopically both grew predominantly as papillary adenocarcinoma (Figs. 8 and 9). Neither was associated with duct hyperplasia.

From these cases and the one surgical case cited in which pleomorphic carcinoma began in the wall of a cystadenoma, it seems likely that in the pancreas cystadeno-

TABLE 2.—*Salient Data of Fourteen Unusual Pancreatic Carcinomas* *

	Pleomorphic	Papillary	Adeno-acanthoma	Mixed
Cases	3	2	5	4
Male	2	2	3	2
Female	..	..	2	2
Ages, yr.	62, 66, 78	49, 57	57, 60, 65, 70, 77	41, 64, 70, 71
Origin				
Ducts	..	2	5	3
Acini	1	..	..	..
Ducts and acini	..	..	..	1
Indeterminate	2	..	..	..
Duct hyperplasia	..	1	2	1
Site				
Undetermined	..	..	..	1
Head	2	2	2	1
Body	..	..	1	..
Head and body	1	..	1	..
Tail	..	..	..	1
Head, body, tail	..	..	1	..
Size range, cm.	4-10	4	6-13	1-16
Invasion				
Perineural lymphatics	1	1	4	1
Ducts	..	1	2	1
Blood vessels	2	1	..	2
Metastases †				
Liver		7		
Lungs		6		
Lymph nodes		6		
Peritoneum		2		
Pleura		2		

* One ciliated adenocarcinoma discussed in text.
† Also one each of adrenal, bone, duodenum, heart, kidney, and muscle.

carcinomas may undergo progressive dedifferentiation and, therefore, may not remain recognizable as such a type at autopsy. Similar behavior has been suspected in the malignant degeneration of some ovarian and thyroid cystadenomas.

EXPLANATION OF FIGURES 2-3-4

Fig. 2 (# 135722).—Pleomorphic pancreatic carcinoma, illustrating the variation in cell size, the large irregular nuclei, and the prominent nucleoli. × 500. All sections stained with hematoxylin and eosin.

Fig. 3 (#51 A 80).—Compression of some cells of a pleomorphic carcinoma into elongated shapes simulating sarcoma. The commonly abundant, finely vacuolated cytoplasm is shown. × 500.

Fig. 4 (#51 A 80).—Central region of the same pleomorphic pancreatic carcinoma, with portions of adenocarcinoma below, mucus secretion and pleomorphic foci at upper right. × 175.

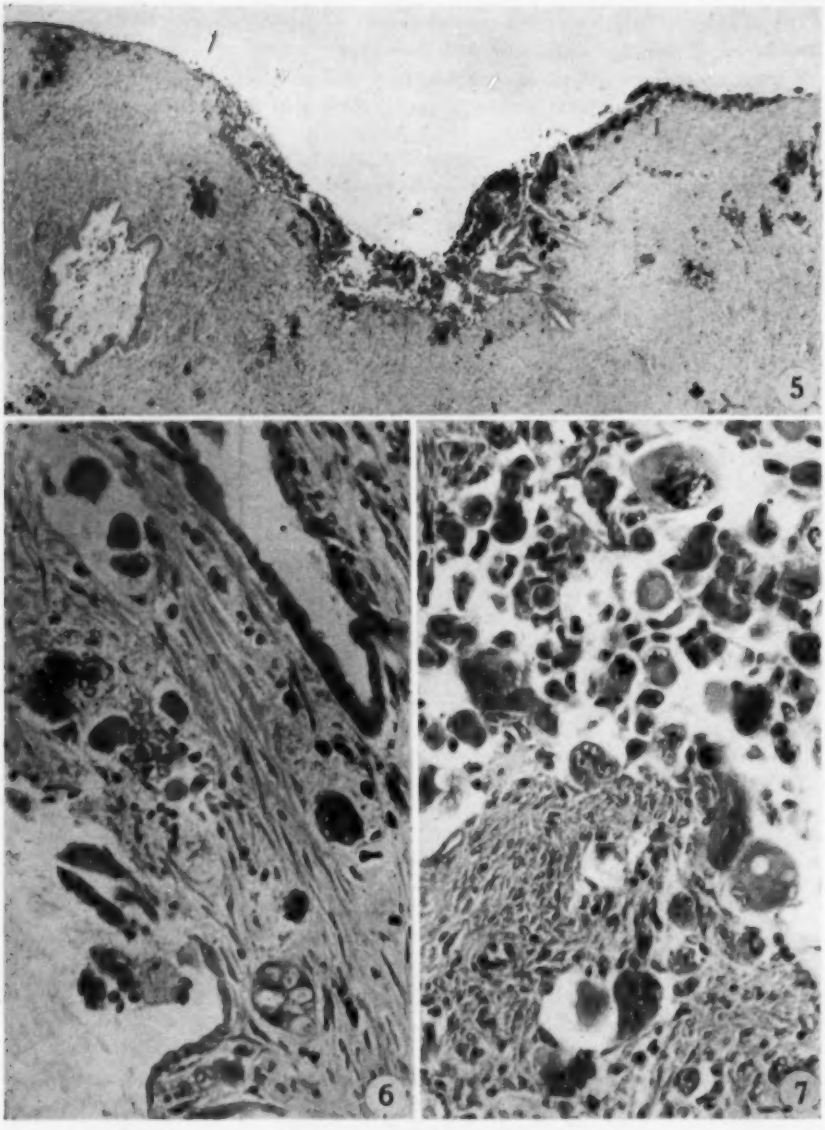


Fig. 5 (#126081).—View at low-power magnification of part of the wall of a pancreatic cystadenocarcinoma surgically removed. All sections stained with hematoxylin and eosin. × 34.

Fig. 6 (#126081).—Foci of pleomorphic carcinoma cells found in the stroma and lymphatics of the cystadenocarcinoma illustrated in Fig. 5. × 275.

Fig. 7 (#128721).—Appearance of the pleomorphic carcinoma found in an abdominal wall recurrence four months later, from the same patient as that in Figures 5 and 6. × 275.

Papillary Adenocarcinoma.—Grossly these tumors were not distinguished from conventional types of pancreatic carcinoma. Microscopically # their growth was characterized by formation of abundant papillary stroma projections covered by malignant epithelium, usually well oriented and often columnar (Fig. 10). As a group, they were of distinctly less than average malignancy (Table 2).

Four cases of conventional duct adenocarcinoma with scirrhous stroma also had foci of papillary growth. As judged by invasion and metastasis, they behaved like ordinary pancreatic carcinomas, in which no papillary foci were found at autopsy.

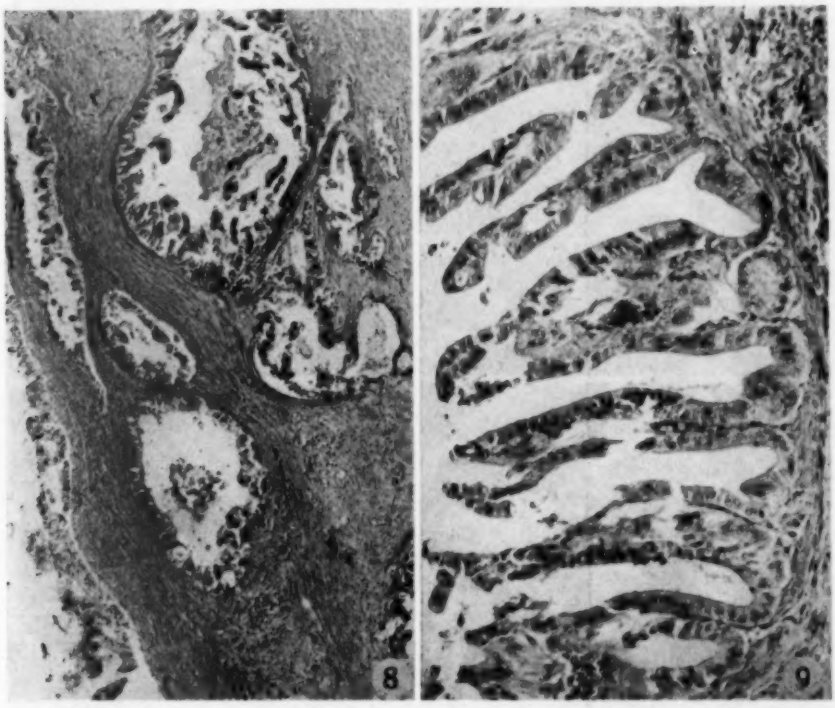


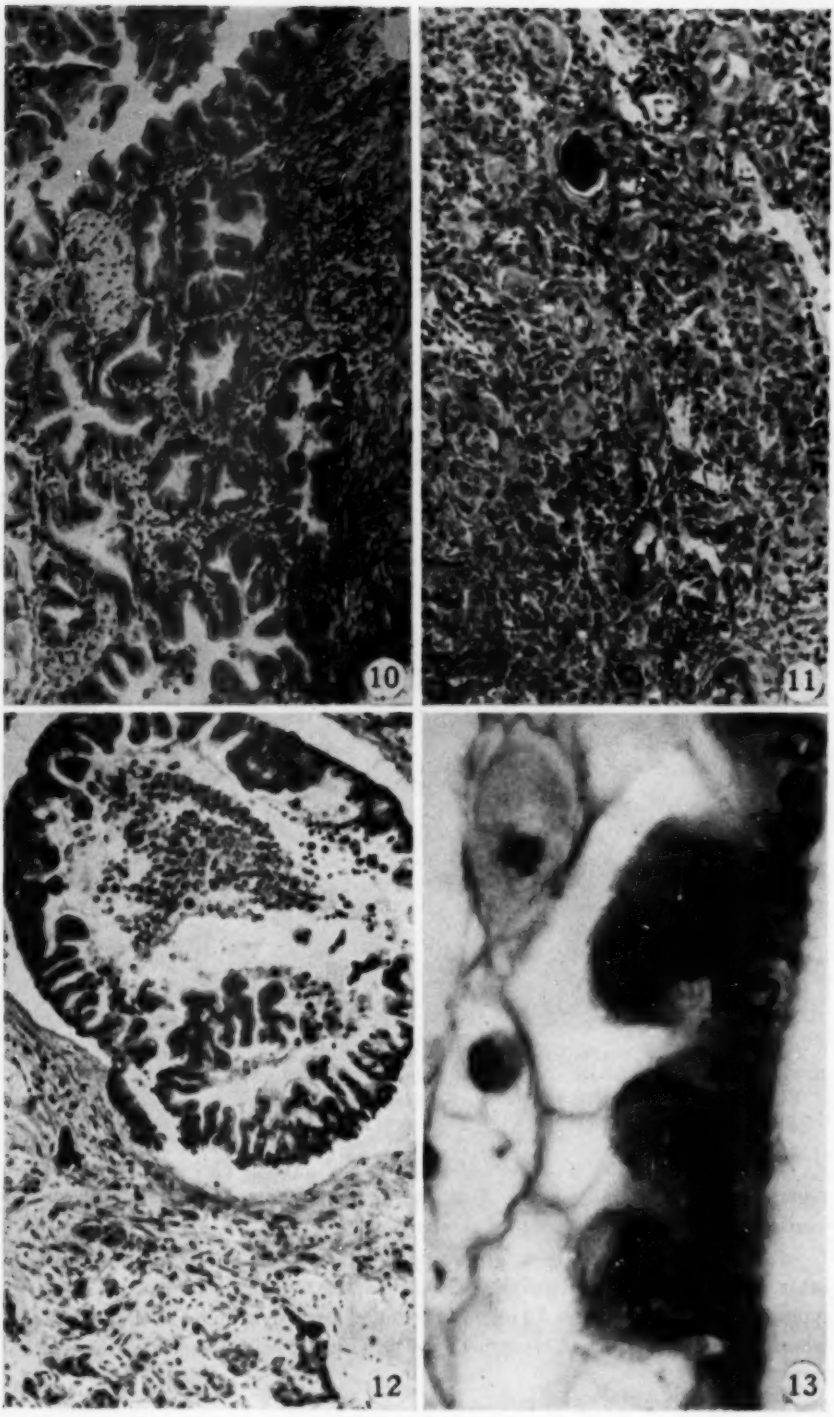
Fig. 8 (#86797).—Invasion of the wall of a pancreatic cystadenocarcinoma by malignant glands with secretory activity. All sections stained with hematoxylin and eosin. × 50.

Fig. 9 (#86797).—Another area of the same tumor as that shown in Figure 8, to illustrate the predominantly papillary growth. × 100.

No focal calcifications or psammoma bodies were observed. These bodies have been reported in papillary pancreatic cystadenocarcinomas,[16] as well as in pulmonary, ovarian, and thyroid neoplasms of similar architecture.

Adenoacanthoma.—In their gross appearance, tumors of this type resembled other pancreatic cancers. Histologically, associated with a glandular carcinoma of typical duct type, there were found nests of squamous cells with intercellular bridges, whorling, and formation of keratinized pearls (Fig. 11). The squamous metaplasia

References 13 and 20.



Figures 10 to 13

(See legends on opposite page)

developed in neoplastic cells, and at times there was an equal admixture of the two types of growth.* Neoplastic behavior was, in general, similar to that of ordinary pancreatic adenocarcinomas, with frequent lymphatic invasion (Table 2).

Ciliated Adenocarcinoma.—One instance of this type was recognized in the head and body of the pancreas of a 69-year-old woman. Aside from the ciliated cells, the tumor had the structure of an ordinary adenocarcinoma of duct origin (Figs. 12 and 13). Metastases were found in the lungs and right adrenal gland. A separate primary carcinoma of the thyroid was found at autopsy. The tumor was identified microscopically near the head of the pancreas, growing along ducts, and with perineural and blood vessel invasion. A similar case is referred to briefly in Mallory's textbook.[24]

Ciliated cells in pancreatic ducts are not mentioned in standard textbooks of embryology and histology. Examination, however, of 25 available surgical cases of aberrant pancreas showed scattered ciliated cells in the large ducts in 3. Examination, also, of the embryonic pancreases of six fetuses of from 12 to 18½ weeks' gestation age (6.0 to 13.5 cm. crown-rump lengths) revealed occasional ciliated cells, particularly in the larger ducts which penetrated the duodenal muscularis. A few cilia were observed in 10 of the total 140 autopsied cases of pancreatic carcinoma reviewed for this purpose.

Mixed Carcinoma.—In four additional tumors were demonstrated mixtures of the unusual growth patterns discussed above. Two represented the combination of cystadenocarcinoma with papillary carcinoma,[17] already considered, and one of these included areas growing as pleomorphic carcinoma.[15] Adenoacanthoma was mixed with papillary [22] and pleomorphic carcinoma in one case each (Table 2).

COMMENT

Study of a large collected group of autopsied cases of pancreatic cancer has proved advantageous in permitting the recognition of a number of carcinomas with unusual growth patterns. It became evident that duct, acinar, and islet epithelial cells, alone or in combinations, could each become carcinomatous. The usual adenocarcinoma of duct type appeared commonly to be accompanied by, and likely was preceded by, pancreatic duct hyperplasia. A separate study of the same series of autopsies showed in 41% of cases a peripheral hyperplasia of pancreatic ducts, associated in 4 cases with carcinoma in situ.[25] This duct hyperplasia has been suggested as a likely precursor of the commonest type of pancreatic carcinoma. What stimulates pancreatic duct hyperplasia is unknown, and the basis of the unusual growth patterns is equally mysterious.

* References 21 to 23.

EXPLANATION OF FIGURES 10 TO 13

Fig. 10 (#104752).—Papillary adenocarcinoma of pancreas, arising from duct epithelium. All sections stained with hematoxylin and eosin. × 150.

Fig. 11 (L. L. 53-2022).—Adenoacanthoma of pancreas, metastatic to liver, from the surgical specimen of a man 65 years old, provided by Dr. Olga Leary. The mixed squamous and glandular pattern is shown. × 150.

Fig. 12 (#130002).—Well-differentiated partly papillary adenocarcinoma of pancreas, including some ciliated cells. × 150.

Fig. 13 (#130002).—From the same case as that in Figure 12, demonstrating the cilia present in this adenocarcinoma. × 1,000.

All the unusual types of neoplasms considered have been previously described. Of the 15 unusual cases involved, 4 possessed more than one of the less common histologic structures. In two this represented the evolution of papillary adenocarcinoma from a malignant cystadenoma. Such a combination is common also in ovarian and thyroid neoplasms of cystadenocarcinoma type. In the other two cases adenosquamous and pleomorphic patterns were mingled with, or appear to have developed from, papillary carcinomas. These findings would emphasize that untreated malignant cystic and papillary pancreatic tumors are prone to become transformed into more highly invasive types of carcinoma.

The squamous metaplastic type of cancer growth is met so commonly among glandular carcinomas of the endometrium, salivary glands, and elsewhere that its appearance in pancreatic carcinoma would not be unexpected. Pure squamous pancreatic carcinomas have also been reported.†

Pleomorphic carcinoma, or carcinosarcoma, would appear to be a late anaplastic flowering of a pancreatic cancer of relatively long duration. Its cytology suggested an acinar origin in two instances. One reason for emphasizing this entity is to direct attention to the pancreas in cases of wildly anaplastic metastatic cancer, since in the instances reported a recognizable, better-differentiated adenocarcinoma or cystadenocarcinoma was present therein. Had adequate microscopic examination of the pancreas not been made, the cases would likely have remained classified as instances of atypical malignant melanoma, myosarcoma, hepatoma, or choriocarcinoma.

SUMMARY

A pathologic study was made of 142 autopsied cases of pancreatic carcinoma. Some carcinomas were believed to have originated from duct, acinar, or islet epithelial cells or from combinations of these elements. Fifteen of the pancreatic carcinomas had unusual histologic patterns of pleomorphic, cystadenocarcinomatous, papillary, adenoacanthoid, ciliated, or mixed types. The unusual structural patterns are described and illustrated to facilitate their pathologic diagnosis.

† References 23 and 24.

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ATYPICAL ENDOMETRIAL CHANGES ASSOCIATED WITH THE PRESENCE OF CHORIONIC TISSUE

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THE PURPOSE of this paper is to describe certain endometrial changes which occur in the presence of chorionic tissue and which, it is thought, result from the hormonal activity of this tissue. Although these alterations are not infrequent, we have been unable to find any study of their characteristics or any mention of them in a survey of current textbooks of pathology.* Only a few references have been found that we think deal in part with the problem to be discussed. Deelman,[6] in his "Die Histopathologie der Uterusmucosa," called attention to some endometrial patterns which occur in cases of uterine abortion and which can be confused with neoplastic growths. Deelman explained these atypical endometrial patterns on the basis of inflammatory-degenerative effects, a point of view that observations reported here do not support. Ferguson [7] called attention to a possible source of error in the cytological diagnosis of vaginal smears in cases of abortion or syncytial hyperplasias of endometrium. In these conditions, he states, glands with marked variations in cellular size and staining quality are frequently found. No details of the histological features of these cases or interpretation of the lesions is given. Aguero,[8] in an extensive study on the histology of endometrial abortion, comments that in some cases the endometrial mucosa shows alterations characterized by "enlargement of the glandular cells with, perhaps, associated proliferative phenomena." He believes that pregnancy and inflammation may have played a role in the pathogenesis of this atypical change. Aguero refers to a case of chorioepithelioma in which "the cells of the endometrial glands showed a monstrous size and aspect" in a degree "not found in any description." He seems to think that "abnormal and exaggerated endocrine influences" could be implicated in the pathogenesis of these lesions.

Before the origin of the trophoblastic tissue had been thoroughly understood, those workers supporting the concept of maternal origin referred to syncytial changes in the endometrium during pregnancy, which are, undoubtedly, in some respects related to the alterations herein described.

As will be seen later, the alterations shown by the endometrial cells are such that they not only may be a source of error in cytological diagnosis or lead to confusion in the histological interpretation, but also, as will be demonstrated with illustrative cases, may be of value in making a presumptive diagnosis of the pres-

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* References 1 through 5.

ence of active chorial tissue in cases in which the chorial material is not in a position accessible to the curette. Furthermore, this study furnishes an opportunity to link hormonal mechanisms to the interpretation of the pathogenesis of some non-neoplastic atypical nuclear alterations which occur in several organs.

MATERIAL

The present study is based on pathological material from 182 cases of uterine abortion, 26 cases of hydatidiform mole, 14 cases of chorioepithelioma, and 4 cases of syncytial endometritis. Reference will be made also to one case of ectopic pregnancy. The material has been taken from the files of the Department of Anatomical Pathology of the Faculty of Medicine of Lima and from the Pathology Laboratories of Memorial Center for Cancer and Allied Diseases of New York. For the most part, routine slides have been used, but in a few cases additional sections were prepared. All the slides were stained with hematoxylin and eosin.

UTERINE ABORTION

Secretory activity and decidual reaction are the fundamental endometrial changes related to the presence of placental tissue. Referring to the endometrial alterations during pregnancy, Novak [5] says:

> In the event of pregnancy the hypertrophic and secretory changes of the pregravid phase become even more marked, so that there is an insensible transition between the premenstrual picture in the nonpregnant woman and the very early decidua of the woman in whom the ovum has been fertilized. In fact, it is not always easy to make the distinction in the laboratory unless embryonic elements, such as villi, are present in the section. The glands of the decidua present marked saw-tooth convolution and scalloping, and the epithelium is low, pale-staining, and actively secretory. At a little later stage the tortuosity of the glands is much less and the epithelium becomes very flat, so that there may be difficulty in distinguishing the glands from lymphatics or venules.

The same author, when discussing the histology of postabortive endometritis, states:

> What has been said as to the qualified significance of the decidual cells applies even more to the gland pattern. Here again the predecidual reaction of the non pregnant woman may produce a high degree of tortuosity and secretory activity of the glands, so that they cannot be distinguished from those of very early pregnancy.

The present study demonstrates that frequently in cases of abortion there are not only epithelial and glandular changes which are an exaggeration of the normal secretory phase but, in addition, alterations with certain specific characteristics which do not occur in the normal endometrial phases. It is common, for instance, in most of the cases showing viable chorionic tissue to find markedly secretory endometrium which on close examination reveals in some glands the presence of groups of cells that are larger than their neighbors. This cellular enlargement exceeds the normal variations occurring in the endometrial cycle and is due, principally, to a nuclear hypertrophy. When this change in size is slight, it occurs more frequently in the vicinity of zones of implantation, and minimal or mild alterations are easily overlooked. In other cases, however, the cellular enlargement is both marked and widespread, although the more accentuated changes always tend to occur focally. These focal alterations are the ones which will be described in some detail. Secretory change, usually exaggerated, with simultaneous proliferative activity of variable degree and cellular enlargement, principally of the nuclei, are main histological features which occur in these areas displaying maximum

change. When extreme secretory activity is combined with an equally great proliferative effect, one sees groups of glands with very vacuolated, foamy cells, which are practically without lumens (Figs. 1 through 4). Here and there are cells with hypertrophic nuclei, sometimes monstrously enlarged and hyperchromatic. Usually these enlarged nuclei show variations in shape, some being lobulated or elongated while others assume more bizarre forms. In some fields the hypertrophic nuclei are predominant, but in others they are less conspicuous, and here the secretory and proliferative changes are outstanding. When the secretory activity is mild or moderate but the proliferative effect intense, cellular masses are formed

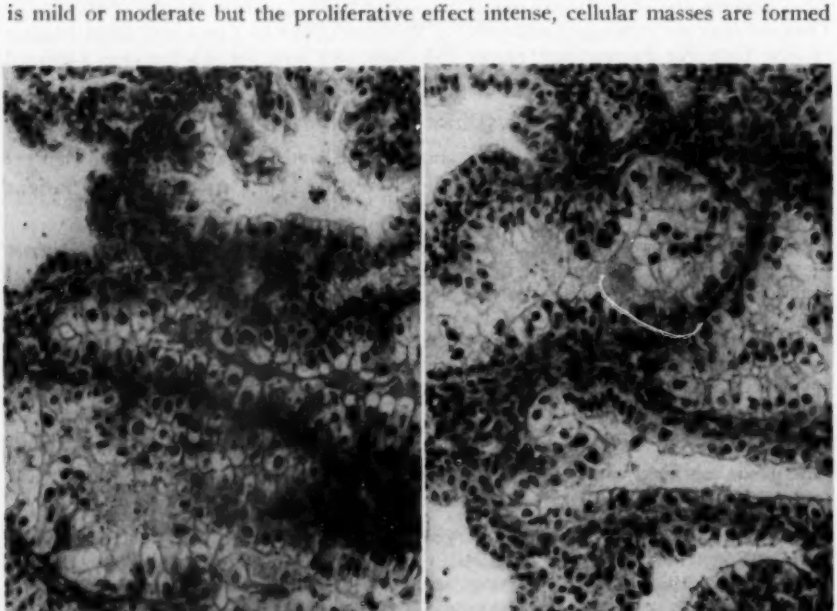


Fig. 1 (Loayza Hospital, # 7001).—Endometrial abortion. Focus of atypical change. Marked secretory activity, cellular reduplication, and nuclear hypertrophy are shown. × 98.

Fig. 2 (another field from # 7001).—Note the contrast between a normal gland, in the lower left corner, and the altered glands. × 98.

which by fusion of their cytoplasm develop a syncythial appearance. As in uterine abortion, there is almost always an associated endometritis, and the presence of inflammatory cells, exudate, and secondary alterations lead to the interpretation that the gigantic nuclei may result from secondary degenerative phenomena. It seems, indeed, that when intensive, the inflammation does influence the histological pattern, contributing to glandular distortion and increased nuclear stainability. A careful analysis, however, of early and intermediate phases of the process in cases free from inflammatory changes leads to the conclusion that the nuclei become

hypertrophic primarily for reasons other than the inflammatory degenerative reactions. The concomitant intensive secretory and proliferative activities suggest, rather, a unique form of overstimulation.

In some cases nuclear enlargement occurs in glands which are histologically closer to the normal proliferative pattern, in other words, in glands with minimal or no secretory activity. The nuclear membrane is then well defined, and the more or less dispersed chromatin is clearly shown (Fig. 5). It is possible to see in one part of a gland some evidence of secretion and in another part frankly proliferative

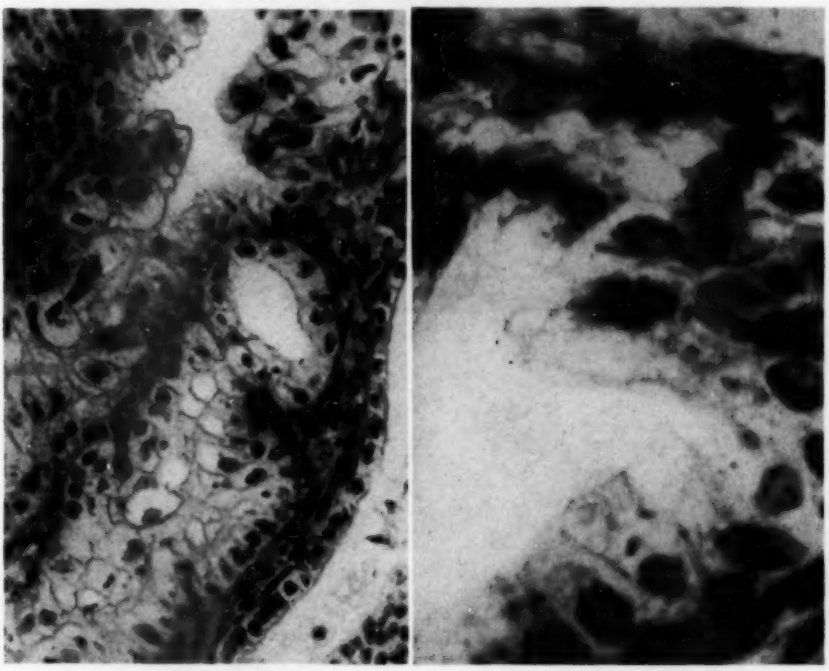


Fig. 3 (Loayza Hospital, # 7001).—Enlarged hyperchromatic nuclei are seen. × 200.

Fig. 4 (Loayza Hospital, # 7001).—Nuclear enlargement, cellular reduplication, and secretory activity are demonstrated. A distinct mitosis can be noted. × 600.

activity and cells with enlarged nuclei. It may have to be stressed that by enlarged nuclei is meant nuclei of sizes which are not present in the phases of the normal endometrial cycle. Another interesting feature observed in these glands is the loss of cellular polarity. The nuclei lie without any orientation, in the most disorderly and capricious ways. A single hypertrophic nucleus may occur between others having normal appearance.

As has been previously said, these changes usually occur focally. However, the alterations can occasionally be the dominant pattern throughout a given section. When the changes mentioned are minimal, there may be no cellular reduplication

or notable secretory activity, and only the presence of some pyknotic, hypertrophic nuclei is observed (Fig. 6). The surface epithelium can undergo similar change, enlarged cells occasionally being present at this level.

As a rule, the remainder of the endometrium shows a secretory or mixed pattern, with areas of definite proliferative change. The stroma displays a variable

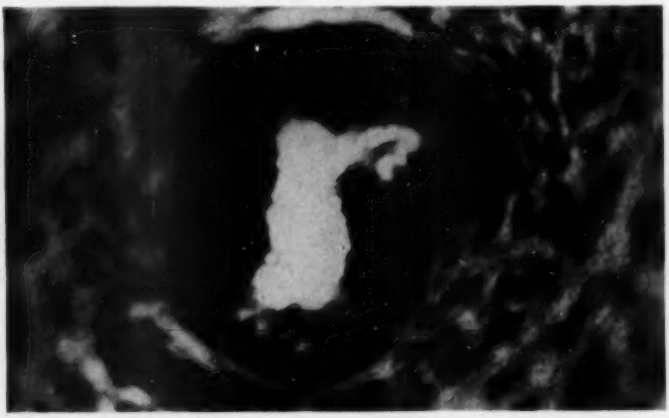


Fig. 5 (Loayza Hospital, #2301).—Endometrial abortion. Nuclear enlargement in gland of proliferative type. × 440.

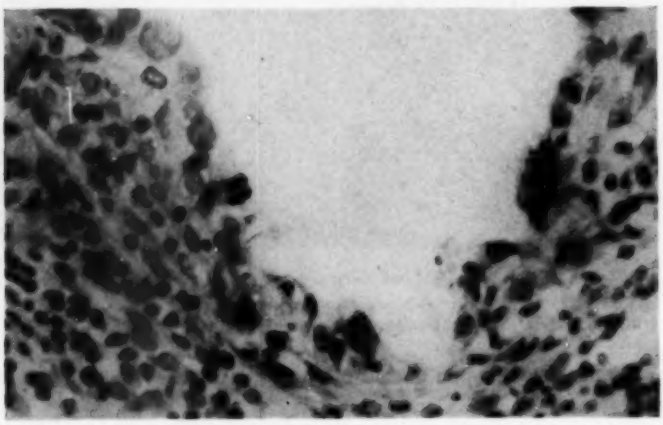


Fig. 6 (Loayza Hospital, #7590).—Endometrial abortion. Minimal secretory activity, discrete nuclear enlargement, and mitosis are present. × 320.

degree of decidual reaction. In the cases with marked change, there is frequently an intensive decidual reaction and the presence of decidual giant cells.

In those instances in which there were striking alterations, it was the rule to find viable chorionic villi with a variable degree of focal proliferation of the trophoblastic layers. In none of the cases showing the more impressive changes were the

alterations associated with the presence of completely atrophic, fibrosed, or hyalinized villi. When there was a minimal chorial activity, the changes were correspondingly less in degree.

A history of metrorrhagia occurring 20 to 60 days prior to the curettage was usually elicited in those cases showing marked changes. Very conspicuous endometrial alterations occurred in 20 of the 182 cases studied.

When one studies the endometrium immediately after an abortion, he may find the glandular alterations discussed here in the absence of villi. It is evident, therefore, that the endometrial changes described may serve as a diagnostic clue in this clinical setting.

ECTOPIC PREGNANCY

A review of the reported findings in the endometrium associated with ectopic pregnancy † reveals that no particular attention has been focused on the occurrence

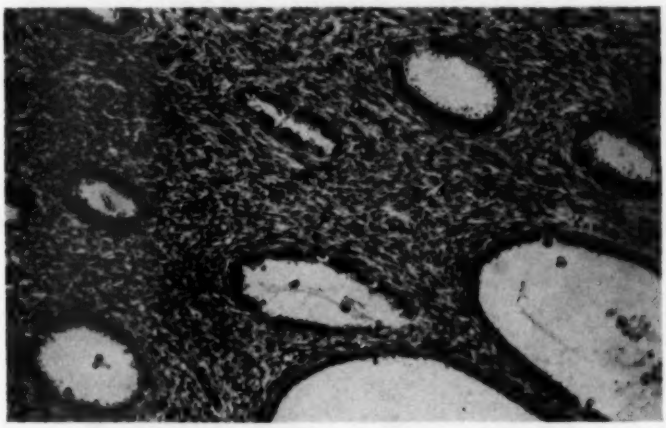


Fig. 7 (Loayza Hospital, # 2120).—Tubal pregnancy. General aspect of the endometrium. Proliferative and cystic dilated types of glands showing occasional enlarged atypical nuclei can be seen. Observe absence of decidual change. × 84.

of cellular and glandular changes described in the preceding section. That this does happen is demonstrated by the following case.

Z. F., 34 years of age, was admitted to the Loayza Hospital of Lima on Oct. 26, 1950, complaining of slight metrorrhagia since her last menstruation, Oct. 4. Physical examination revealed a moderately anemic patient with hemorrhagic vaginal discharge, enlarged uterus, and painful left adnexa, in which an elongated mass was palpated. A partial hysterectomy, with removal of both tubes and ovaries, was performed on Oct. 31.

Pathological study revealed an ectopic pregnancy in the left tube. The chorionic villi were lined by both trophoblastic layers and showed occasional areas of slight syncytial proliferation. A large, mature corpus luteum was present in the left ovary. The uterus showed no striking gross change. The histological examination was, however, of interest. The endometrial glands presented a mixed and atypical pattern. In areas the glands were of a definite proliferative type, with tall cells

† References 9 through 11.

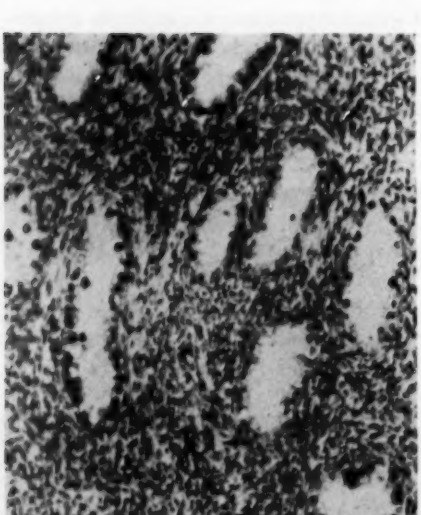


Fig. 8 (Loayza Hospital, # 2120).—Another view in greater magnification, showing the bizarre, atypical nuclei dispersed in disorderly fashion in practically all the glands in this field. Note loss of polarity.

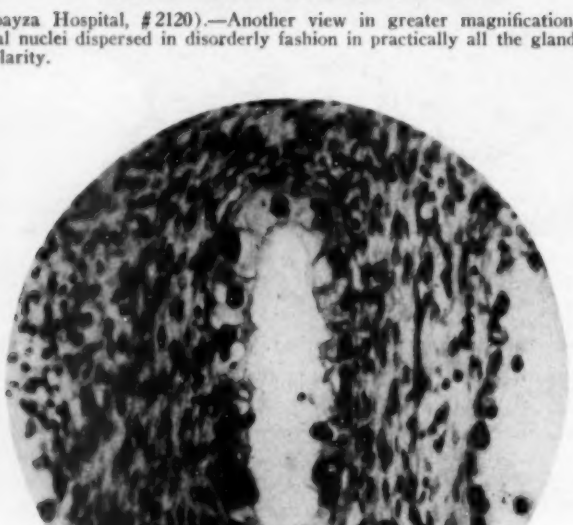


Fig. 9 (Loayza Hospital, # 2120).—Another view, showing nuclear change and moderate secretory activity.

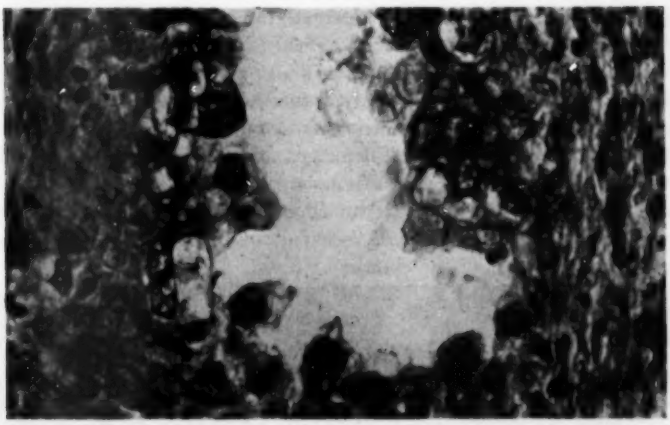


Fig. 10 (Loayza Hospital, # 2120).—Gland showing marked secretory effect, nuclear enlargement, and cellular reduplication, with slight syncytial tendency. × 480.

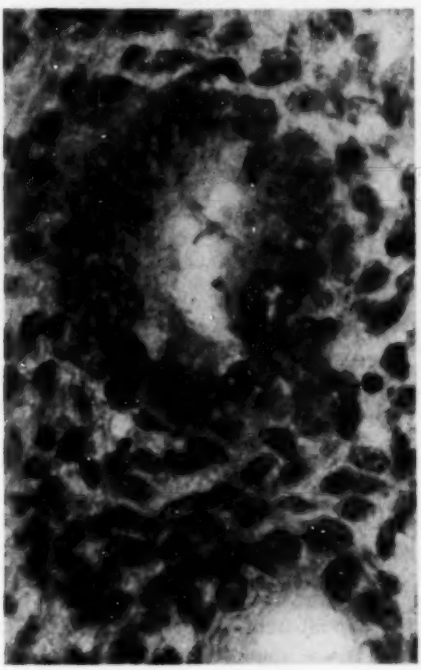


Fig. 11 (Loayza Hospital, # 2120).—Gland showing single gigantic nucleus. × 440.

showing deep-staining nuclei, marked reduplication, and numerous mitoses. In other zones, but to a much smaller extent, the glandular pattern was frankly secretory, with vacuolated cells, marked infolding, and intraluminal budding. Gland dilatation with formation of cysts was also noted. Large or limited portions of the glands in these areas presented atypical cellular changes. These portions were characterized by a cellular enlargement due to nuclear hypertrophy and cytoplasmic vacuolation. The cells appeared deformed and filled with vacuoles of different diameters and in more advanced stages showed breakdown of the protoplasmic membrane. The nuclei were enlarged to from three to four times the size of the normal cells and were round, ovoid, vesicular, or capriciously distorted (Figs. 7

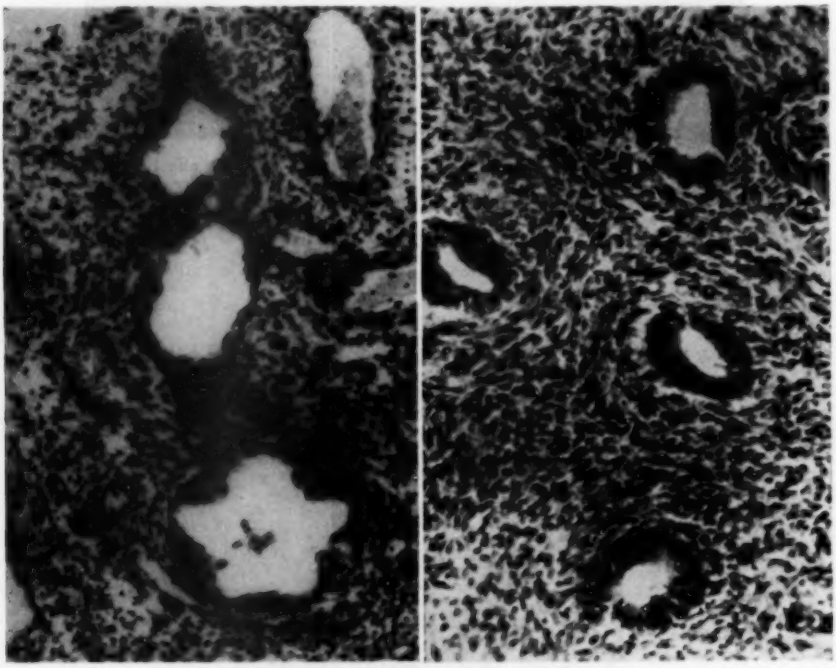


Fig. 12 (Loayza Hospital, #419).—Endometrial biopsy specimen. Scattered enlarged pyknotic nuclei in glands showing secretory pattern. Note edematous stroma without decidual reaction. See text.

Fig. 13 (Loayza Hospital, #419).—Surgical specimen. Areas of endometrium showing normal proliferative pattern.

through 9). The chromatin was hyperchromatic and condensed in thick bars or granules. Rarely, a nucleolus was seen in the enlarged atypical cells. In the same gland, it was possible to see all transitions from the normal cells to those slightly altered or very atypical. It was common to find areas in which the atypical cells had proliferated and formed several layers with loss of nuclear polarity. The cellular reduplication tended to be directed toward the lumens. Syncytial masses of vacuolated cells were also formed (Fig. 10). The nuclear hypertrophy was better demonstrated in those areas showing less secretory effect (Fig. 11). Occa-

sionally, mitoses were seen in the atypical cells. The stroma was mostly cellular and dense, as in the normal proliferative phase; in rare areas it was slightly edematous. No evidence of decidual reaction was found. Occasional foci of mononuclear cell infiltration were noted.

The changes described involved the surface and medial portions of the endometrium. In the deep zone they were minimal or absent.

Several interesting points can be deduced from this case. The nuclear enlargement, as well as the proliferative and secretory changes, was readily apparent. In view of the absence of conspicuous inflammation, the possibility of its playing a role in the genesis of the changes is unlikely. In addition, this case clearly indicates that for the production of the glandular alterations, it is not necessary that chorial tissue be present in the uterus itself. This suggests, rather, a humoral influence.

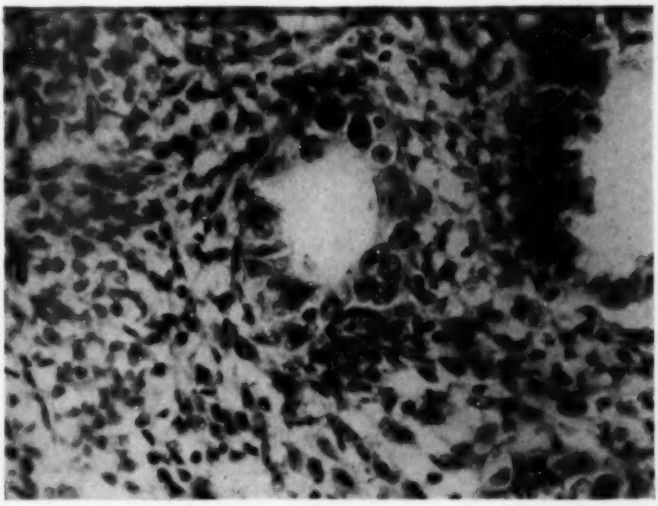


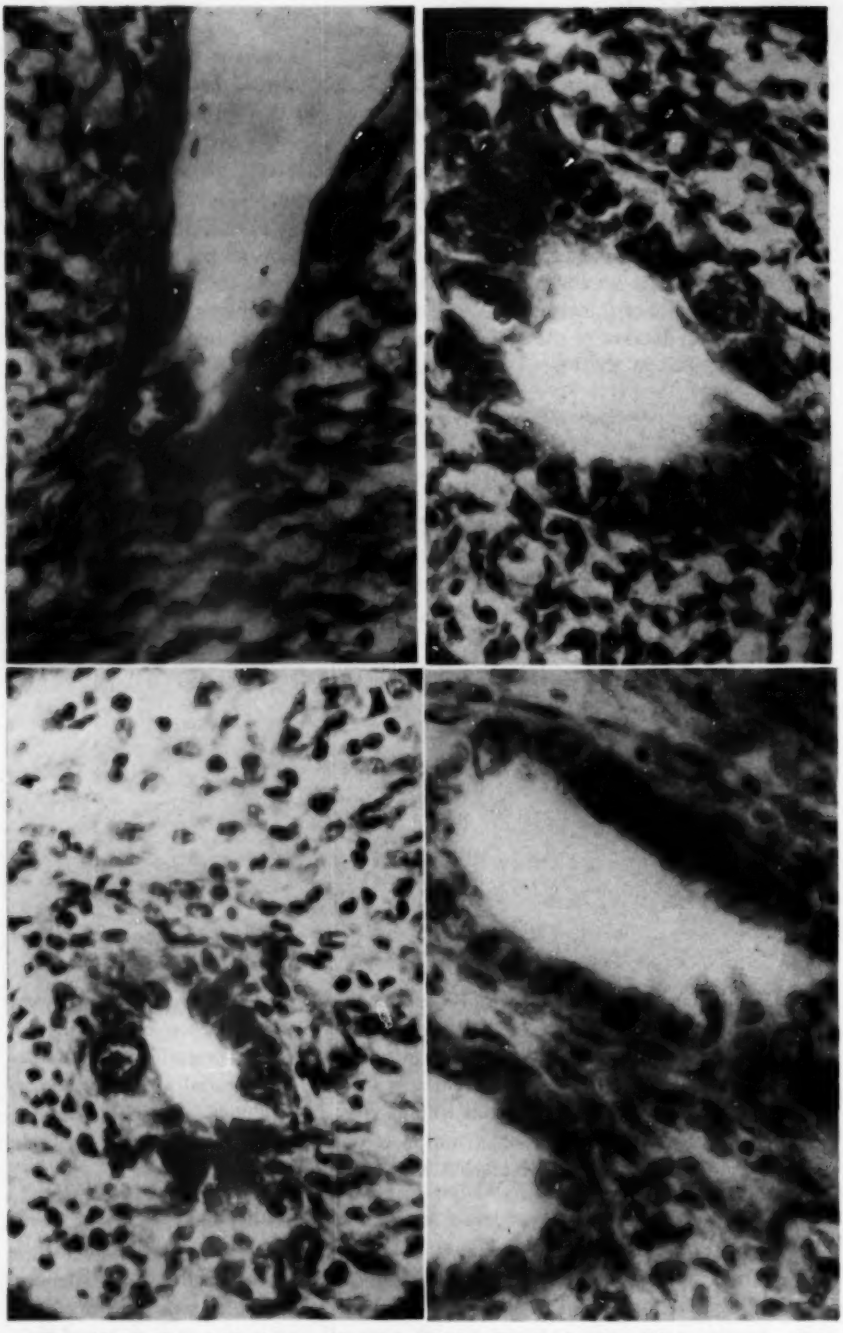
Fig. 14 (Loayza Hospital, #419).—Gland showing atypical proliferative pattern. Cellular reduplication, loss of polarity, and marked nuclear enlargement are present.

Since the stroma revealed no trace of decidual transformation, this case shows that the glandular alteration can be dissociated from its occurrence in the uterus. Finally, in this case the uterus was studied in the absence of significant manipulation, which is not the case in the usual specimen of endometrial abortion. Hence, the possible influence of endometrial trauma may be excluded.

A reinvestigation of the endometrium in ectopic pregnancy directed to verifying the frequency of this kind of change is desirable.

HYDATIDIFORM MOLE AND CHORIOEPITHELIOMA

Changes similar to those previously described occur also in the endometrium in cases of benign hydatidiform mole, in the so-called chorioadenoma destruens, and in cases of chorioepithelioma. Here, too, were found varying degrees of alterations, ranging from cases in which the glandular lesions were more or less diffuse throughout the endometrium to those in which the change was limited to a single



Figs. 15, 16, 17, and 18 (Loayza Hospital, #419).—Glands showing different aspects of the atypical proliferative pattern. Gigantic nuclei are prominent in all the photomicrographs.

focus. In six cases of chorioadenoma destruens, three of benign hydatidiform mole, and two of chorioepithelioma, endometrial changes of impressive degree were found. In one case of chorioadenoma destruens, six cases of benign hydatidiform mole, one case of chorioepithelioma, and two of syncytial endometritis, they were moderate or slight. The secretory component was present in variable proportions but was, as a rule, moderate and not so prominent as in the cases of abortion. Here, on the contrary, the proliferative change and nuclear enlargement may be remarkable, giving rise in instances to problems of interpretation. As a matter of fact, our attention to this whole problem was directed by the following case, illustrative of the alterations found in this group.

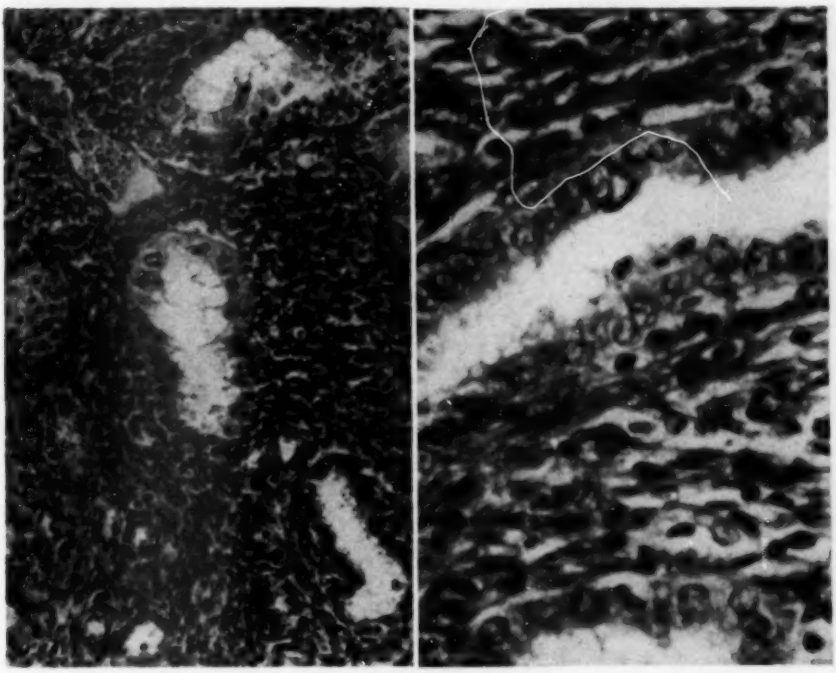


Fig. 19 (Memorial Hospital, # L-800).—Chorioadenoma destruens. General view of the endometrium, showing scattered, moderately enlarged nuclei in several glands. Stroma shows no trace of decidual reaction. × 98.

Fig. 20 (Memorial Hospital, # L-800).—Gland showing an atypical gigantic nucleus between normal cells. There is slight secretory activity. × 440.

A. A., 24 years old, had a spontaneous abortion in Jan. 1949, delivering a hydatidiform mole at the Maternity Hospital of Lima. In the latter part of May, 1949, the patient complained of metrorrhagia, which increased in intensity, necessitating hospitalization on June 11, when she entered the Loayza Hospital of Lima. On admission, she was markedly anemic, and the gynecological examination disclosed a slightly enlarged uterus. On June 18, a Galli Mainini reaction (frog test) was strongly positive, suggesting the presence of chorial tissue. Thereafter, a curettage was performed. This failed to reveal any chorial tissue in the uterine cavity. The glands were of secretory type, with moderate infolding. The stroma was edematous, but no trace of decidual reaction was seen. The striking alteration consisted of a disorderly cellular enlarge-

ment of individual cells, or groups of them, involving practically every gland. The hypertrophied nuclei were intensely hyperchromatic and of variable forms. In general, the cells were arranged in one row, but in areas there was slight reduplication. The cytoplasm showed moderate vacuolation (Fig. 12). At that time we were unable to arrive at any conclusion concerning the endometrial changes, and no definite diagnosis could be given. Nevertheless, on the basis of the positive biological test and the antecedent of molar abortion, a hysterectomy was performed seven days after the curettage. The pathological study revealed a uterus 9 cm. in length and 5 cm. in transverse diameter. In the anterior and right lateral walls, there were several well-defined, somewhat friable, hemorrhagic nodules, situated intramurally, without relation to the endometrium. The largest of these nodules measured 1.5 cm. A large mature corpus luteum was present in each ovary.

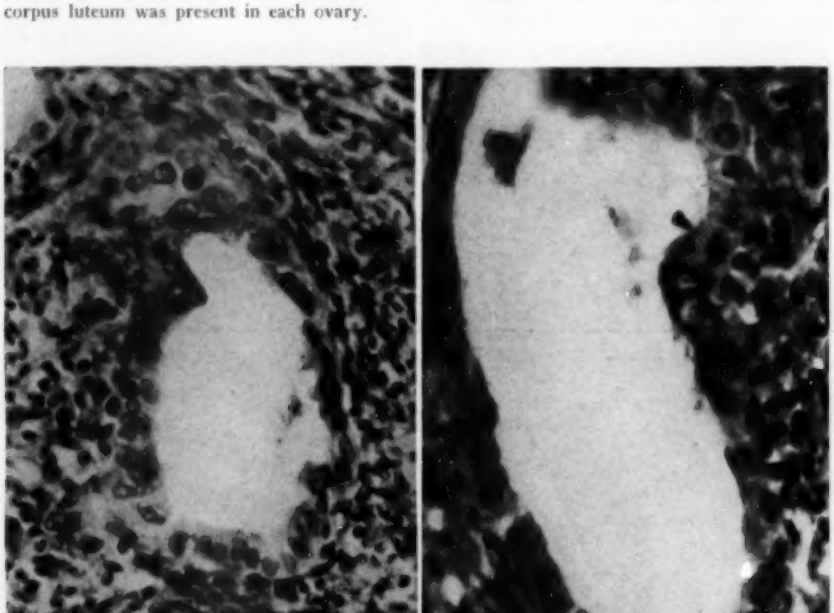


Fig. 21 (Loayza Hospital, # 1000).—Chorioadenoma destruens. Glands show several atypical enlarged nuclei. × 312.

Fig. 22 (Loayza Hospital, # 1000).—Another gland presenting similar aspect to that in Figure 21. × 440.

The histological examination of the uterus showed that the nodules were nests of chorial tissue with proliferation of syncytial and Langhan's cells intermingled with hydropic chorial villi. Invasion of the myometrium in the vicinity of the nodules, necrosis, and tumor permeation into the vessels were noted. In general, the pattern was that of molar rests, with marked intramural penetration and moderate trophoblastic proliferation. In its entirety, the endometrium presented an abnormal pattern. The glands showed mostly a proliferative pattern, but in areas they were slightly dilated and moderately hyperplastic, and in a very few fields minimal evidence of

secretory effect could be demonstrated. In the areas showing a normal proliferative type of reaction, the cellular reduplication in the glands and the mitotic activity were intense (Fig. 13). The striking change consisted of a tremendous cellular enlargement of isolated cells involving most of the glands (Figs. 14 through 18). This enlargement was due basically to hypertrophy of the nuclei, which appeared intensely hyperchromatic, vesicular, lobulated, or bizarre in shape. Aggregations of enlarged, proliferated glandular cells were frequently seen, in which mitosis could be detected only occasionally. In the cell accumulation, the presence of gigantic, monstrous nuclei was striking. In areas the impression was obtained that

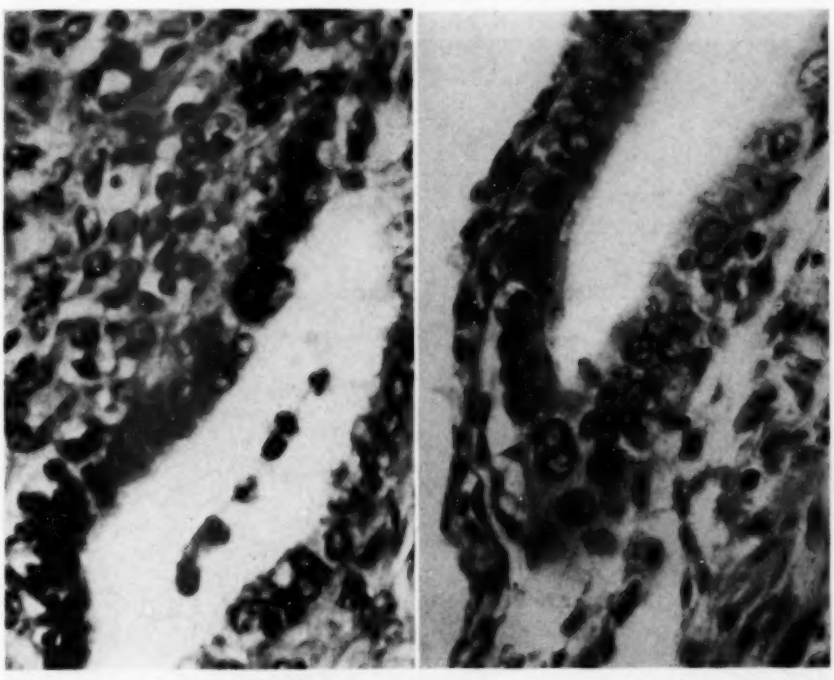


Fig. 23 (Loayza Hospital, # 1083).—Benign hydatidiform mole. Single hypertrophic, atypical nucleus in gland showing moderate secretory activity. × 440.

Fig. 24 (Memorial Hospital, # 52-3874).—Chorioadenoma destruens (?). Single well-preserved, enlarged, active nucleus is demonstrated. × 440.

these nuclei were the result of some form of swelling, but in others definite increase in the chromatin with well-defined nuclear outlines was apparent. In the dilated glands, epithelial desquamation and amorphous intraluminal secretion were noted. Throughout, the stroma was cellular, rather dense, and without trace of decidual reaction. Only occasional minute foci of mononuclear infiltration were seen. In no area was invasion of the endometrium by trophoblastic cells observed. Figures 19 through 26 show similar changes in other cases.

It should be observed that the changes can occur independently of the decidual reaction and inflammation.

Although our report is based on study of routine slides and, therefore, does not furnish appropriate material for a definite statement, it is our impression that in some cases, even with a marked degree of trophoblastic activity, these changes may be absent. At least in one case of hydatidiform mole and one of chorioepithelioma, representative areas of endometrium were available for study in which no conspicuous alteration was seen. We cannot, at the present time, establish the reasons for these differences. It is possible that the degree of hormonal activity would be one explanation.

It can be pointed out that these changes may, besides the importance of their pathogenetic interpretation, have practical value, as demonstrated in the case related.

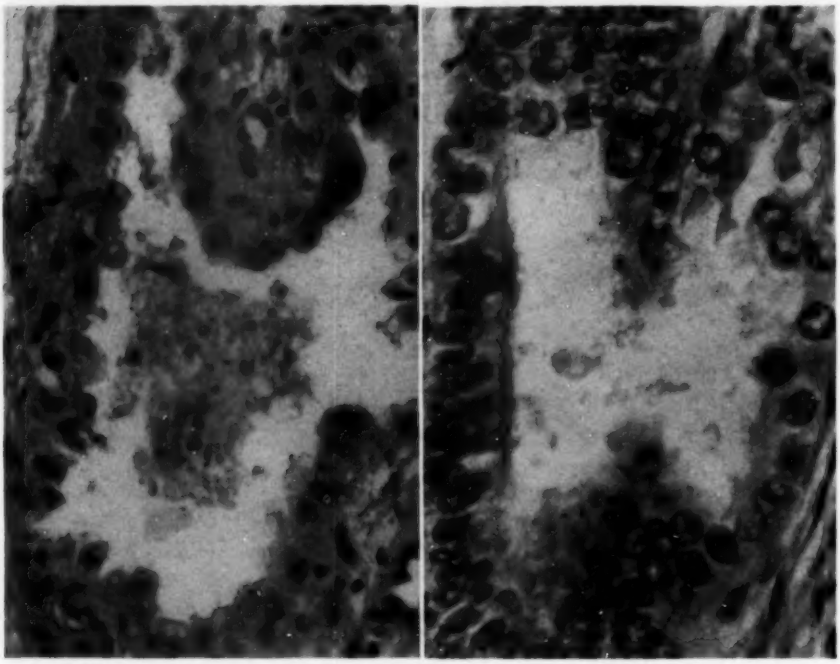


Fig. 25 (Memorial Hospital, # L-531).—Chorioadenoma destruens. Nuclear enlargement in secretory glands; marked decidual reaction. × 230.

Fig. 26 (Memorial Hospital, # P-6668).—Chorioepithelioma. Gigantic nucleus and evidence of proliferative activity. × 400.

It is well known that on occasions the nodules of chorioadenoma destruens or chorioepithelioma can be intramurally situated, out of the sphere of the endometrial biopsy. An indirect proof of the presence of active chorial tissue can be obtained by the finding of lesions such as those described in the endometrium. This is more significant if we recall that the biological tests, undisputedly the more valuable diagnostic tools, can be, on occasion, of a low, dubious titer, or even negative, in the presence of hydatidiform mole or chorioepithelioma.‡

‡ References 12 and 13.

COMMENT

We have described the different modalities of some endometrial changes associated with the presence of active chorial tissue in the uterus or in other locations. Fundamentally, the alterations are characterized by an irregular nuclear hypertrophy of glandular cells and a variable proliferative activity. As we have seen, the proliferative phenomena occur even in the presence of a diverse degree of secretory effect. It seems that these changes are unrelated to the decidual reaction of the endometrium, as they have been seen in the presence or the absence of this type of stroma. Similar alterations have not been observed in the phases of the normal endometrial cycle. Although in some cases the changes are diffuse and very conspicuous, as a rule they are focal and in instances so discrete that they can be found only after a specific search for them. Frequently, the lesions are more or less masked by the inflammation. However, when one is familiar with the change, it is easy to recognize the subordinate role played by this factor in the histological picture. The presence of active or proliferative chorial tissue has been the common denominator in all the cases showing distinct changes. However, it is important to recall that it appears that marked trophoblastic proliferation is also possible without associated endometrial alteration.

The focal pattern of the lesion is not surprising, since it is well known that even in the normal endometrium we are apt to find areas of different responsiveness to hormonal stimulation.[5]

Our study does not allow a definite statement to be made about the pathogenesis of the changes described. From the illustrations in this paper, it appears clear that they cannot be explained as inflammatory or degenerative. As we have shown, they can occur when the inflammation is minimal or absent. The invariable presence of active chorial tissue suggests immediately a relation to the pathogenesis. It seems provocative to postulate that the chorionic hormones and estrogens would be, in some way, responsible. The proliferative and secretory activities are likely to be the result of the kind of action which normally produces these effects. It seems that there is some factor interfering in the process of interphasic growth, with resultant formation of gigantic polyploid nuclei. Since only appropriate experimental evidence can shed definite light on this problem, we avoid, at this time, a more detailed discussion of the probable pathogenetic mechanism involved.

We have been impressed by the similarity of the phenomena of nuclear enlargement in some of our cases and the changes produced in the normal endometrium after irradiation. Here, the nuclear hypertrophy is very conspicuous, and even proliferative activity in the glands can be detected. We cannot elaborate further on the meaning of this similarity, we merely mention the observation.

In several organs connected with the endocrine system, nuclear alterations of benign character, usually characterized by marked hypertrophy, occur frequently (thyroid, parathyroid, seminal vesicles, etc.). On the basis of the observations here reported, it would appear advisable to study the possibility of hormonal actions as responsible for those changes.

SUMMARY

A description of some atypical endometrial patterns occurring in the presence of chorionic tissue in the uterus or in other anatomical locations is given. The alterations are characterized by an irregular nuclear hypertrophy of isolated glandu-

lar cells, usually accompanied by a marked proliferative activity, together with simultaneous secretory change of variable degree. The alterations tend to occur focally and are apparently unrelated to the decidual reaction of the stroma. The chorionic tissue was present as placental rests showing viable villi, benign hydatidiform mole, chorioadenoma destruens, or chorioepithelioma. The enlarged atypical nuclei frequently display a gigantic size, and the resultant histological pattern is one never seen in the normal endometrium and in extreme cases may give rise to a problem of interpretation, among the possible diagnoses being the suspicion of carcinoma. It is apparent that desquamation of these atypical nuclei may lead to error in the cytological diagnosis of vaginal smears. The alterations are, on the other hand, a histological clue to the presumptive diagnosis of the presence of active chorial tissue in those cases in which the chorionic material is not in a position accessible to curettage in the endometrial biopsy.

It is suggested that the atypical endometrial pattern may result from the hormonal activity of the chorionic tissue.

Dr. F. W. Stewart, Dr. F. W. Foote, and Dr. R. C. Mellors assisted me in the preparation of this paper. Dr. S. Spitz showed me several cases of endometrial abortion, which added much to my understanding of the lesions here reported.

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HISTOPATHOLOGY OF AMINO ACID DEFICIENCIES

III. Histidine

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EXPERIMENTAL studies of the morphological effects of specific amino acid deficiencies have been reported in an attempt to link these deficiencies to particular tissue responses. The present report is the third in a series concerned with the histological effects of such deficiencies. An earlier paper by Schwartz, Scott, and Ferguson [1] described reversible histological alterations of the testes, thymus, accessory sex structures, anterior pituitary, and adrenals in rats fed a diet totally deficient in phenylalanine. Later, Scott and Schwartz [2] reported similar types of responses following threonine deficiency but with no effect upon the adrenals. The latter investigation utilized an approach to the study of the pituitary basophiles which revealed that, while the thyrotrophic hormone producing basophiles were not modified, the gonadotrophic hormone producing basophiles were completely depleted. In 1946, Maun, Cahill, and Davis [3] described morphological changes in rats deprived of histidine. Since many of our observations and some techniques differ from theirs, the results are being presented.

METHODS

Young male Sprague-Dawley rats were divided at random into three groups. One group of three rats (normal-control) received a purified diet containing 19 crystalline amino acids, vitamins, sucrose, cottonseed oil, and the necessary salts as described by Rose, Oesterling, and Womack.[4] A second group of 12 rats (deficient) were fed the same ration, complete in every respect except for the total lack of histidine. The third group of 10 rats (starved-control) were pair-fed the complete diet so that their consumption of food was equal to that of the deficient rats. All animals were kept in individual cages and, with the exception of the pair-fed group, were fed ad libitum. At the end of 42 days all rats except two of the deficients were killed by exsanguination under ether anesthesia. The two deficient rats, which were not killed at this time, were placed on the complete diet for recovery observation and killed 45 days later. At autopsy the adrenals, testes, and pituitary of each rat were weighed.

All tissues, with the exception of the pituitaries, were fixed in Bouin's solution and stained with hematoxylin and eosin. The pituitaries were fixed in Zenker-formol and stained by methods described hereafter. For demonstration of the acidophiles of the anterior pituitary, sections were stained with acid fuchsin. Other sections were stained by methods described by Purves and Griesbach * to identify and differentiate thyrotrophic and gonadotrophic basophiles of the anterior pituitary. In using these procedures it was necessary first to treat the sections by a method originated by Gomori [7] and developed by Halmi [8] and to photograph these sections. The same

Dr. Wayne Gutzman did the statistical evaluation of the body and organ weights.

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* References 5 and 6.

sections were then re-treated by the periodic acid-Schiff (PAS) reagents, which method stained all basophiles, and the identical fields were rephotographed. In this manner records of two different techniques were obtained for the same section and field. Comparison of the two photo-

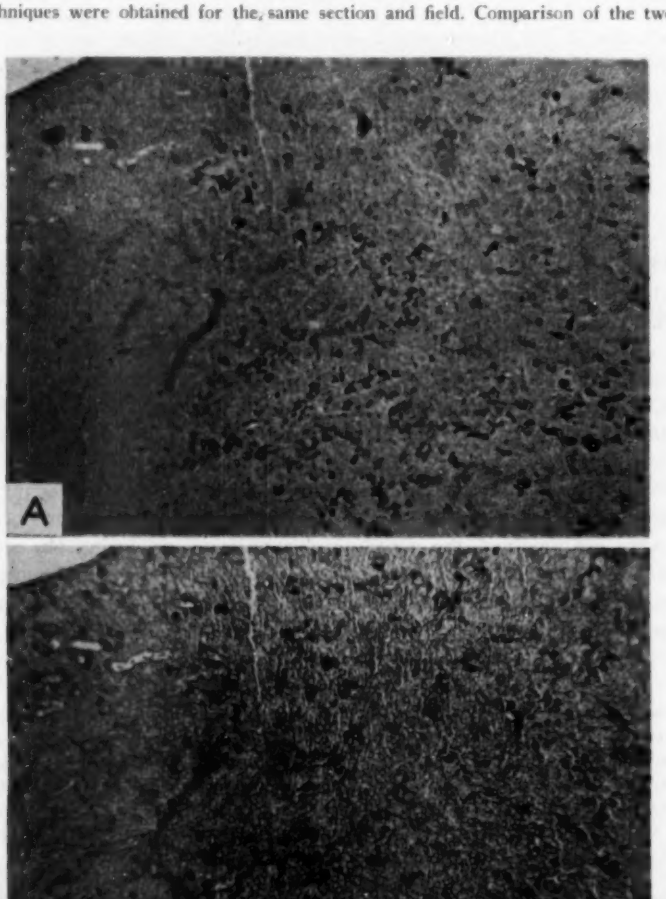

Fig. 1.—*A*, Anterior pituitary of normal-control rat stained by Gomori method. Gomori-positive cells (dark) are thyrotrophic basophiles. *B*, Same section and field restrained by periodic acid-Schiff (PAS) method. All basophiles are PAS-positive. Visual subtraction of the Gomori-positive cells indicates gonadotrophic basophiles. × 100.

graphic records and visual subtraction of the Gomori-positive thyrotrophic cells from the PAS-positive total basophiles permitted identification of the gonadotrophic cells (Figs. 1, 2, and 3).

The weight loss, poor appetite, and unthrifty appearance which is typical of protein deficiency soon was apparent. The final weights of the histidine-deficient

rats were considerably less than those of their pair-fed controls and the normal-controls (Table). The weights of the recovered rats compared favorably with those of the normal-controls.

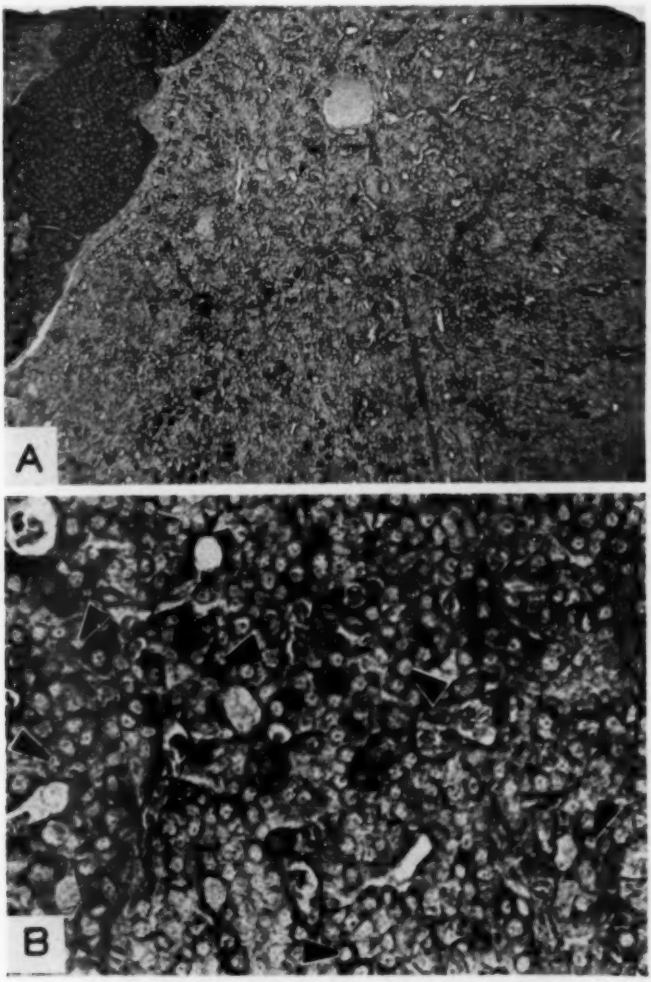

Fig. 2.—*A*, Anterior pituitary of starved-control rat stained by Gomori method to show thyrotrophic cells; × 100. *B*, Same section after restaining by PAS method. Because these gonadotrophic basophiles are fainter than normal and difficult to illustrate under low magnification, they are photographed at a higher magnification; some are indicated by black arrowheads. Very dark cells are thyrotrophic basophiles; × 470.

Pituitary.—Alterations of the cells of the pituitary glands of the histidine-deficient rats were confined to the anterior lobe. These changes were comparable to those observed in the pituitaries of threonine-deficient rats.[2]

Examination of the deficient pituitaries after the application of the Gomori and PAS techniques disclosed that the thyrotrophic basophiles were intact and unaffected but that the gonadotrophic basophiles were completely absent (Fig. 3). In the starved-control rats the thyrotrophic cells likewise were unaffected and the gonado-

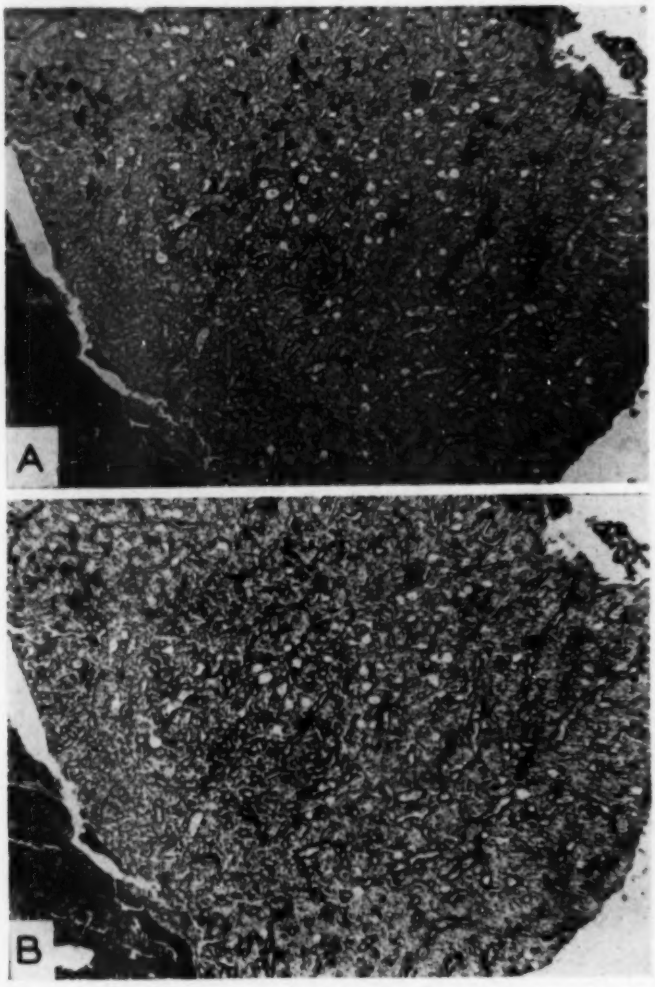

Fig. 3.—*A*, Anterior pituitary of histidine-deficient rat stained by Gomori method to show thyrotrophic basophiles; × 100. *B*, Same section and field restained by PAS method. Only those cells which were Gomori-positive above are PAS-positive below, a fact demonstrating absence of gonadotrophic basophiles; × 100.

trophic cells were still present although reduced in size and less prominent (Fig. 2). Reduction in the size and staining capacity of the acidophiles was distinctive in the deficient rats (Fig. 4 *C*). The principal loss was cytoplasmic, although the nuclei

were small. In the starved-controls, reduction in the size of the acidophiles also was observed, but the decrease was considerably less than in the deficients (Fig. 4 *B*).

Testes and Accessory Structures.—Grossly and histologically, the testes, epididymides, ventral prostates, and seminal vesicles of the histidine-deficient rats

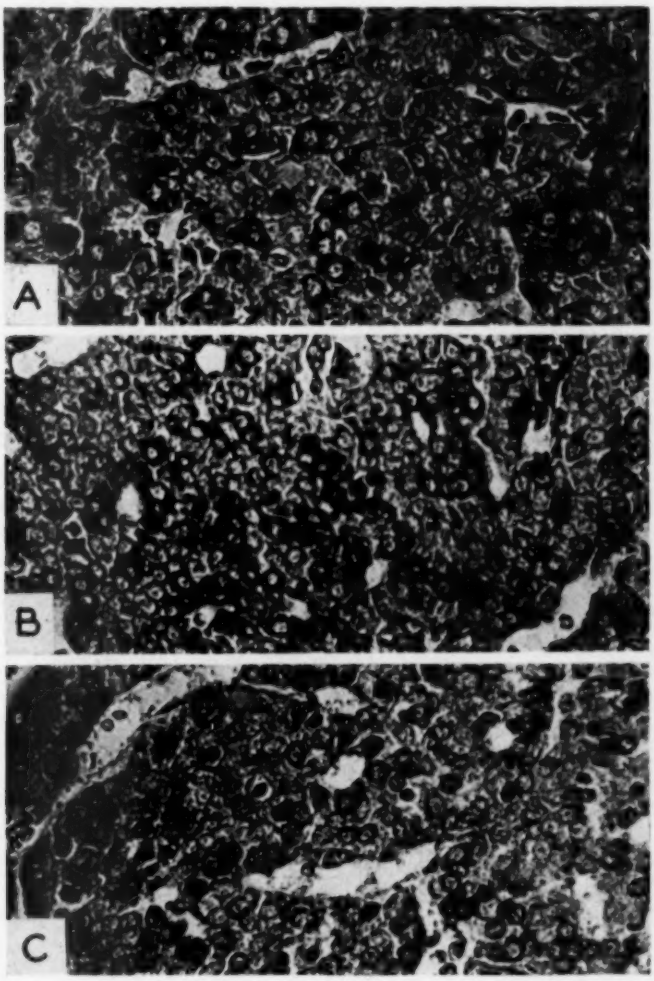

Fig. 4.—*A*, Anterior pituitary of normal-control rat, identifying acidophiles. *B*, Anterior pituitary of starved-control rat. Acidophiles are slightly smaller than normal. *C*, Anterior pituitary of histidine-deficient rat. Acidophiles are very small, with little cytoplasm. Acid fuchsin; × 470.

were very atrophic. Their structure resembled the appearance of these organs following both phenylalanine and threonine deficiencies. The seminiferous tubules were extremely small, being composed principally of supporting cells and spermatogonia (Fig. 5 *C*). The lumens contained numerous free degenerating cells. The

testicular interstitial tissue was likewise atrophic. That the Leydig cells were not functional was evidenced by the histological appearance of the ventral prostates and seminal vesicles. The prostatic and seminal vesicular epithelia were non-secretory and atrophic. The epididymal epithelial cells were crowded; the tubules,

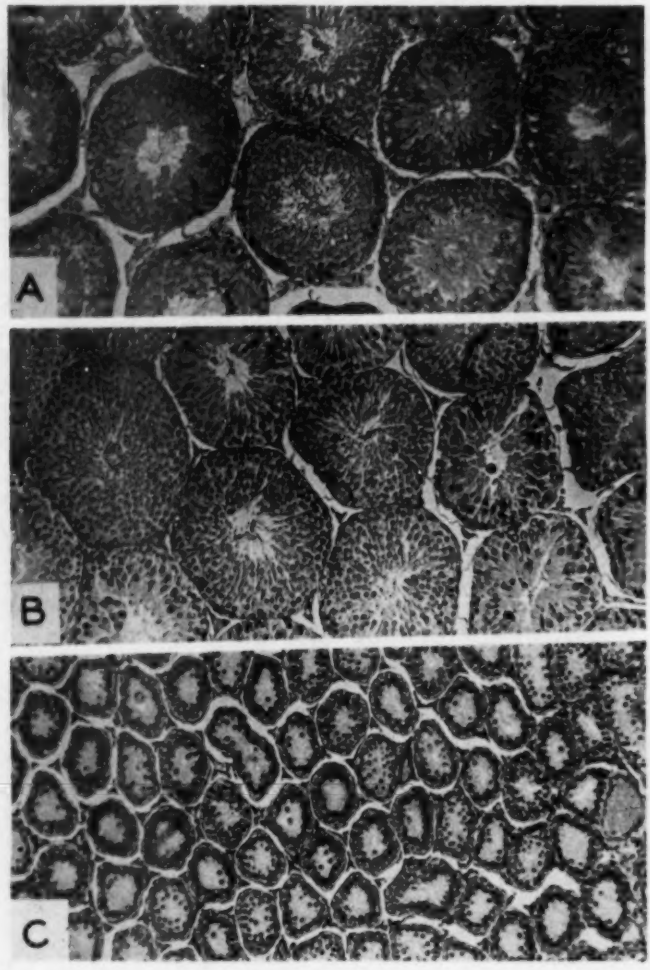

Fig. 5.—*A*, Testes of normal-control rat. *B*, Testes of starved-control rat. *C*, Testes of histidine-deficient rat. Hematoxylin and eosin; × 100.

small. The interstitial connective tissue of all accessory sex structures was vastly increased (Fig. 6*C* and 7*C*).

The testes and related structures of the starved-control rats appeared to have been more lightly affected by restriction of dietary consumption. The testes (Fig. 5*B*) and epididymides (Fig. 6*B*) compared rather favorably in structure with

those of the normal-controls. Spermatogenesis was active, but spermiogenesis lagged considerably. Various stages of spermatid maturation were present in the testes, but no completely mature sperm were seen. The epididymal tubules were filled with degenerating early and late spermatids. The prostatic acini were smaller

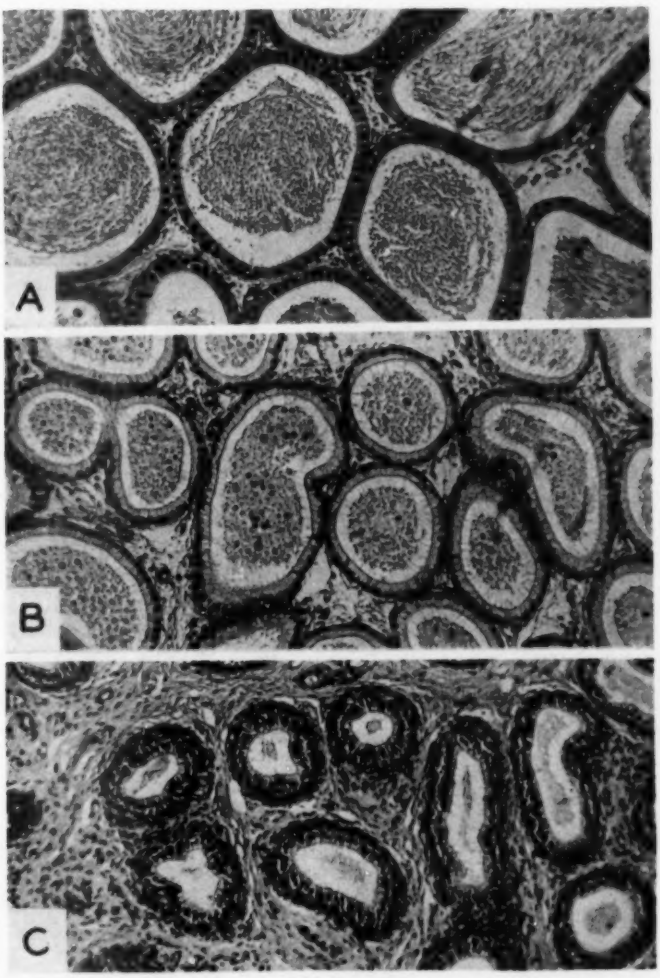

Fig. 6.—*A*, Epididymis of normal-control rat. *B*, Epididymis of starved-control rat. *C*, Epididymis of histidine-deficient rat. Hematoxylin and eosin; × 100.

than normal, composed of flattened epithelium with prostatic secretion present within the acini (Fig. 7 *B*). Increase in connective tissue stroma of the accessory sex organs was minimal in this group of rats.

Adrenal.—Cellular atrophy of the zona glomerulosa was conspicuous in the histidine-deficient adrenals (Fig. 8 *C*). Most of the zona glomerulosa nuclei were

hyperchromic; many, pyknotic. The cytoplasm of many of these cells appeared diminished. This abnormal appearance of the zona glomerulosa was similar to that observed in phenylalanine-deficient rats.[1] The zona fasciculata, zona reticularis, and medullary areas were unaltered structurally. The proportional widths of the

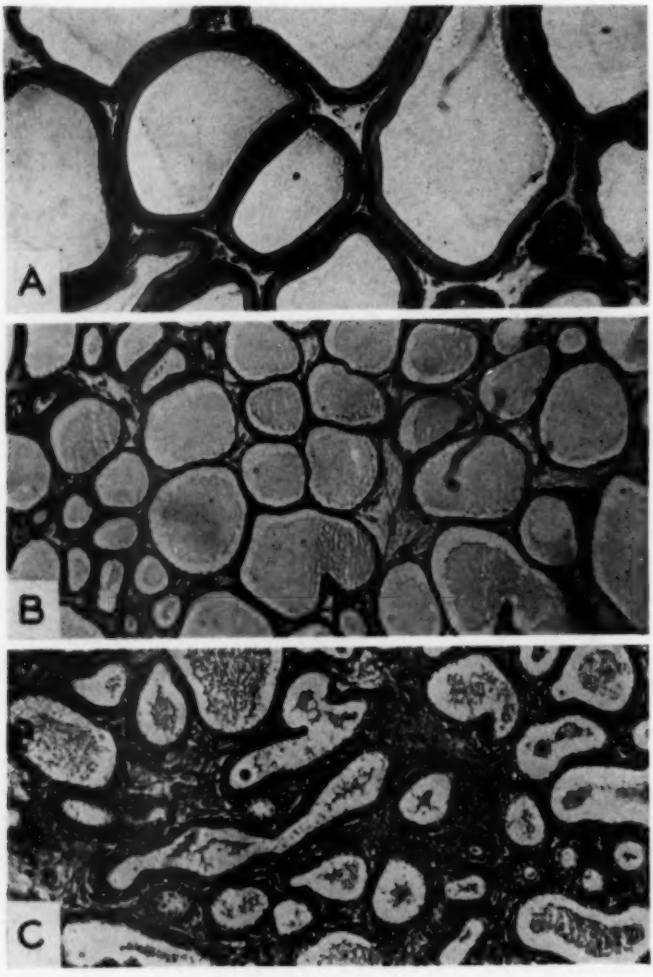

Fig. 7.—*A*, Ventral prostate of normal-control rat. *B*, Ventral prostate of starved-control rat. *C*, Ventral prostate of histidine-deficient rat. Hematoxylin and eosin; × 100.

cortical zones appeared to be normal, although the cortex as a whole was narrower. No histological modification of the adrenals of the starved-control rats was observed.

Thymus.—In 7 of the 10 histidine-deficient rats, no thymus gland could be identified grossly at autopsy. In each of three rats, however, a small atrophic thymus was dissected free. Sections of these organs showed the usual cortical and medullary

regions, but the cortex was thin and the cells loosely arranged (Fig. 9 *C*). In the starved-control rats the thymus was clearly seen at autopsy but was smaller than normal. Histologically, the cortical and medullary zones were reduced, but no modification of the structural organization was apparent. In neither the histidine-

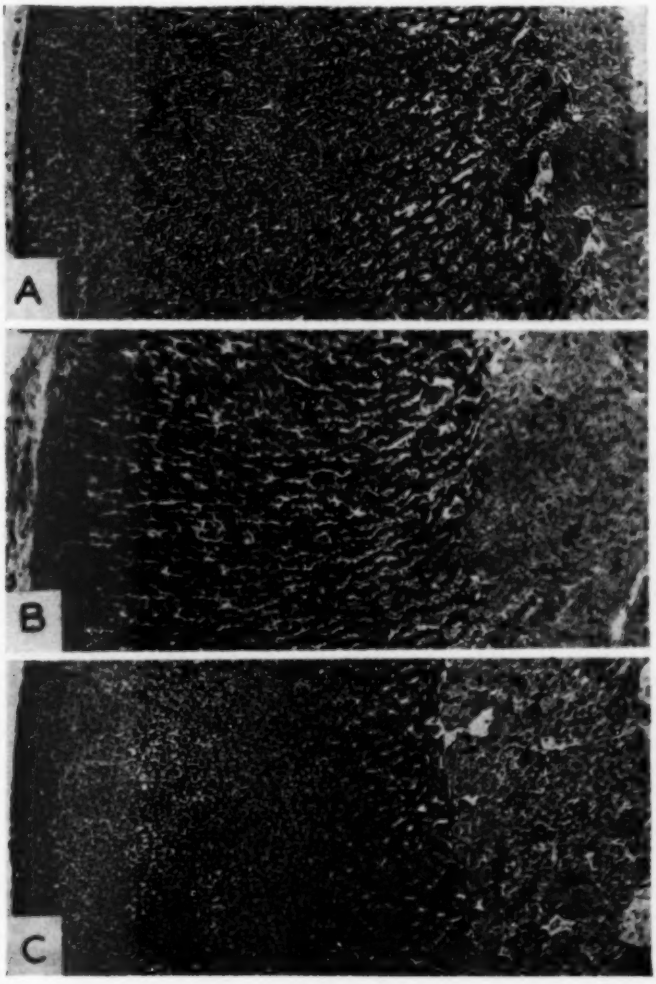

Fig. 8.—*A*, Adrenal cortex of normal-control rat. *B*, Adrenal cortex of starved-control rat. *C*, Adrenal cortex of histidine-deficient rat. Hematoxylin and eosin; × 100.

deficient nor the starved-control thymus glands was there any appreciable proliferation of connective tissue.

Bone.—Observation of sections of the tibia showed that growth had been retarded in the pair-fed controls and interrupted in the deficient rats. The epiphyseal

cartilage plates of the deficient rats were narrow, and bony trabeculae were very small or absent in the diaphysis. In the starved-control rats, the epiphyseal plates were narrower than normal, but the cartilage cells were aligned in long columns and some bony trabeculae were present.

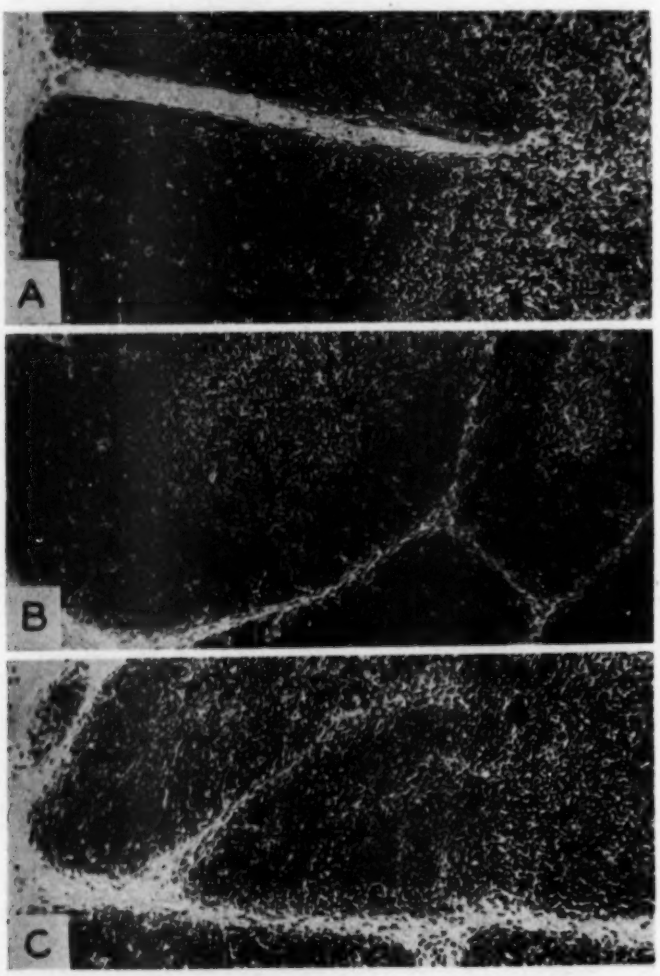

Fig. 9.—*A*, Thymus of normal-control rat. *B*, Thymus of starved-control rat. *C*, Thymus of type found in three histidine-deficient rats. Hematoxylin and eosin; × 100.

Thyroid.—The thyroids of both the deficient and the starved-control rats were smaller than normal, but no significant alteration of the follicular epithelium was observed in either group. The deficient thyroids contained both large and small follicles, many of the latter being without colloid.

Recovery.—The two deficient rats which were placed on the complete diet gained weight. Their tissues were examined histologically at the termination of the recovery period, and no deviation from the normal morphology was observed.

COMMENT

The tissue reactions in rats deprived of histidine were strikingly similar to those which resulted from either phenylalanine or threonine deficiency. Severe testicular, epididymal, prostatic, seminal vesicular, and thymic atrophy were common findings in all experiments. The differences between the effects of partial inanition and those of histidine deficiency were easily distinguishable, since the latter effects were more severe. The intense tissue regression in the deficient rats was due to the superimposition of deficiency effects upon those of partial inanition. The observations reported in the present study differ in many respects from those described by Maun and associates,[3] who had fed rats a histidine-deficient diet. These differences may have been due to the fact that our rats were fed the deficient diet for a longer period. These authors reported that in the deficient rats, when compared with the pair-fed controls, small thymuses persisted, the pituitaries were unaffected, spermatogenesis was delayed, and the testicular interstitial tissue and adrenals presumably were unaltered.

Use of the techniques described showed that the total lack of dietary histidine resulted in total regression of the pituitary gonadotrophic basophiles. The atrophic condition of the seminiferous tubules and the absence of spermatogenesis were manifestations of the complete functional depletion of the gonadotrophic-hormone-producing cells of the pituitary. This conclusion is based upon the fact that the PAS-positive gonadotrophic basophiles in the pituitaries of the recovered rats were normal in size and distribution. The loss of this supportive secretion, in the deficient rats, led to functional failure of the Leydig cells, which, in turn, resulted in atrophy of the accessory sex organs. Partial inanition, on the other hand, caused alteration of the gonadotrophic basophiles to a lesser degree, and secretory activity continued at a reduced level, or rate. This reduction of gonadotrophic hormonal support to the testes and testicular interstitial cells was indicated by the persistence of incomplete spermatogenesis in seminiferous tubules of normal size and the partial regression of the accessory sex structure. The thyrotrophic basophiles were uneffected by either histidine deficiency or partial inanition and were able to give sufficient hormonal support to the thyroids.

The regressive change of the pituitary acidophiles in the histidine-deficient rats was identical to the effects of phenylalanine and threonine deficiencies upon these cells. It appeared that the lack of these amino acids was expressed directly upon the acidophiles, which then failed to supply somatotrophic hormonal support of growth. The acidophiles of the starved-control rat pituitaries were somewhat smaller than normal, but not so seriously effected as in the deficients, and were able to supply some hormonal support. Comparison of the body and organ weights (Table) and the appearances of the epiphyseal cartilage plates of the two groups supports this view. Reference to the Table will show that there appears to be no relationship between the body-weight loss and the weights of the adrenals, testes, or pituitaries. It was evident that the heavier rats lost more weight on the deficient diet than did the lighter rats. This observation may be accounted for by a greater loss of body

fat in the heavier animals. The differences in body and organ weights between the histidine-deficient and the starved-control rats has been determined as being statistically significant at the 0.01 level.

The change noted in the adrenal cortex of the deficient animals was confined to the zona glomerulosa. Similar alterations of this type were observed in the adrenals of rats deprived of phenylalanine.[1] The question of zona glomerulosa regulation via the pituitary or by a distinctly independent "humoral" control, as suggested by Deane and Greep,[2] might be considered for a moment. Our observations

Comparison of Body Weights and Organ Weights of Histidine-Deficient, Pair-Fed Starved-Control, Recovered, and Normal-Control Rats

Rat No.	Body Weight (Gm.)			Organ Weights (Mg.)		
	Start	Final	Change	Adrenals (2)	Testes (2)	Pituitary
		Histidine-Deficient				
69-1	75	45	−30	19.4	191.0	1.6
69-2	74	42	−32	16.8	218.6	2.6
69-3	76	50	−26	33.0	276.8	3.0
69-4	58	38	−20	17.8	131.2	2.4
69-5	54	34	−20	18.0	177.0	3.2
69-6	65	40	−25	17.8	162.0	3.0
69-7	68	44	−24	26.0	181.0	3.2
69-8	74	47	−27	27.4	351.8	2.6
69-9	55	39	−16	26.0	111.6	3.4
69-10	50	44	−14	23.6	131.0	2.6
		Starved-Control				
69SC-1	64	72	+ 8	37.2	1376.8	4.0
69SC-2	65	61	− 4	26.8	1096.8	3.4
69SC-3	57	63	+ 6	27.4	1428.2	3.2
69SC-4	76	81	+ 5	35.0	1875.6	4.2
69SC-5	65	73	+ 8	26.8	1623.0	5.0
69SC-6	69	63	− 6	28.8	1235.0	3.0
69SC-7	73	66	− 7	30.8	1495.8	3.8
69SC-8	72	67	− 5	26.0	1387.8	5.2
69SC-9	70	94	+24	29.4	2052.2	6.0
69SC-10	67	71	+ 4	28.4	956.0	3.0
		Recovered				
69-11R	55	121 (36*)	....	53.8	2610.0	7.2
69-12R	67	118 (35*)	....	49.6	2866.2	9.0
		Normal-Control				
60-69-1	77	207	+130	31.2	2784.4	8.6
60-69-2	62	160	+98	35.2	2491.4	7.4
60-69-3	67	200	+133	32.6	2781.4	8.2

* Weight of these animals at the end of the deficient period when they were placed on the recovery diet.

may offer some support to the latter concept. In the previous study of threonine deficiency,[2] regressive changes of the pituitary acidophiles and gonadotrophic cells were observed. No alteration of the adrenal cortex occurred. In the present experiment, however, similar changes were observed in the pituitary chromophiles, but the adrenal glomerulosae of these rats were affected. It would appear that histidine deficiency has some direct action upon the outer zone of the adrenal which is entirely independent of pituitary influence. No significance could be attached to the narrowing of the adrenal cortex. Since the organs were smaller than normal, one would expect general reduction in the width of this region.

The thymic involution which has been described in the amino-acid-deficient rats may be comparable to accidental terminal thymic involution, which occurs in

humans. The "clinical" status of the deficient rats, other than their general appearance and responses, was not recorded, and it is quite possible that the seven rats in which thymic tissue was not discernible grossly were closer to death than the three rats in which some thymic tissue was seen. The thymus glands of the recovered rats were well developed.

The retrogressive tissue responses observed in this study did not lead to permanent damage, since the tissues in the recovered rats compared favorably with the normal. The tissue reactions were not irreversible pathological degenerations, and, although the deficiency resulted in serious tissue damage, the elements and the potential for full regeneration remained.

SUMMARY

Young male rats were placed on a purified "synthetic" diet which was completely deficient in histidine. Regressive tissue changes occurred in the pituitary, testes and accessory organs, thymus, adrenal cortex, and bone. Replacement of the missing histidine in the diet of deficient rats resulted in complete recovery of the tissues to normal.

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LETTERER-SIWE'S DISEASE

Report of a Case

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AND
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INTEREST in nonlipoid reticuloendotheliosis (Letterer-Siwe's disease) has increased in recent years, since the suggestion by several investigators * that this disease is probably related to the Hand-Schüller-Christian syndrome and eosinophilic granuloma. However, since Letterer's first description of nonlipoid reticuloendotheliosis in 1924,[7] relatively few cases have been reported.

A patient with Letterer-Siwe's disease exhibiting the unusual features of severe liver damage and generalized edema was observed by us and forms the basis for the present report. In addition, this is the first reported case, to our knowledge, in which chemical studies of some of the involved tissues have been attempted.

REPORT OF CASE

J. G., a 2½-year-old Latin-American boy, was admitted to the Children's Hospital of the University of Texas Medical Branch because of abdominal swelling of two months' duration and jaundice and petechiae of three weeks' duration.

The child became ill seven months prior to admission, with the appearance of foul-smelling purulent material on the gums. Local therapy followed by intramuscular injection of penicillin resulted in some improvement, but the condition persisted. Three months later the patient became listless, irritable, and anorexic. The patient's abdomen began to increase progressively in size two months prior to admission, and this condition was soon followed by edema of the lower extremities. Three weeks before admission a petechial rash was noted on the abdomen and back and the patient appeared jaundiced (Figs. 1 and 2). Scrotal edema became marked two days before admission.

The past history revealed a normal pregnancy and birth. The patient was the product of the 11th pregnancy. Birth weight was 9 lb. 8½ oz. (4.3 kg.). The diet had been poor, with inadequate fruits and vegetables and no supplementary vitamins. The only previous illness had been a severe diarrhea at the age of 19 months. There had been no known exposures to infectious diseases.

The family history disclosed no heredofamilial diseases. There were eight normal siblings; two siblings had been stillborn.

Physical examination on admission showed the patient to be ill and pale, with an icteric tint. The temperature was 98 F. (rectally). The pulse was 120 per minute. The patient weighed 31 lb. (14 kg.). The head circumference, 46 cm., and the length, 84 cm., were within the normal limits. The abdominal circumference was 67 cm. The scalp and the anterior upper chest were covered by a greasy, scaly, seborrheic-like dermatitis. Many petechial and purpuric lesions were present on the trunk, neck, and groin and to a lesser extent on the face and extremities. Purulent drainage was observed coming from a perforation in the right drum. The mucous

From the Departments of Pathology and Pediatrics, University of Texas Medical Branch.

* References 1 to 6.

membranes of the mouth appeared jaundiced and pallid. All the teeth were loose. The gingival margins were necrotic, and the breath had a foul odor. Petechial lesions were noted on the mucous membranes of the pharynx. Generalized adenopathy, consisting of enlarged firm, discrete, nontender lymph nodes measuring 1 to 2 cm. in diameter, was noted. The lungs and heart

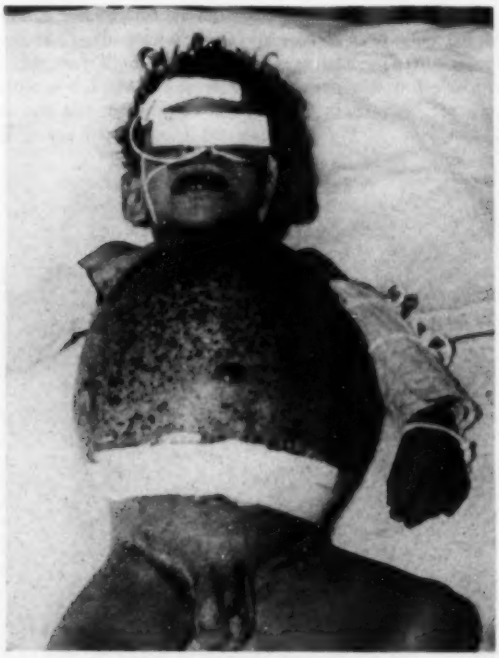

Fig. 1.—Hemorrhagic rash involving trunk, neck, and mucous membranes.

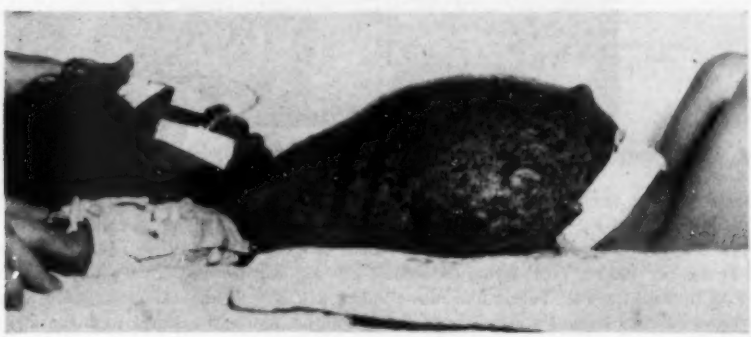

Fig. 2.—Hemorrhagic rash.

were considered normal. The abdomen was protuberant and tense, with 4+ ascites present. The liver, very firm, was palpable 5 cm. below the right costal margin in the midclavicular line. The spleen, also very firm, was palpable 4 cm. below the left costal margin. Four plus edema of the genitalia and lower extremities was present. There was slight pitting edema of the dorsum of the hands and dependent portions of the trunk. The deep reflexes were normal.

Laboratory examinations on entry revealed a blood count of 1,840,000 red cells, a hemoglobin content of 5.6 gm., and 5,000 white cells, with a differential count of 37% active polymorphonuclear leucocytes, 5% stab forms, 54% lymphocytes, 3% monocytes, and 1% eosinophiles. One normoblast was seen per hundred white cells. There were 9.3% reticulocytes and 16,560 platelets per cubic millimeter. The hematocrit reading was 17%, mean corpuscular volume 91 cu. μ mean corpuscular hemoglobin 30.2 $\mu\gamma$, and mean corpuscular hemoglobin concentration 33%. Prothrombin time measured only 10% of normal (Quick's method). Coagulation time (Lee and White) was 40 minutes. Bleeding time was over 15 minutes. Clot retraction was partial in 24 hours. The Rumpel-Leede test was positive. The urine contained 2 + albumin, rare red cells, and 2 to 4 white cells per high-power field. The urine bilirubin test was positive qualitatively and the urobilinogen test negative. Blood Kolmer and Kahn tests were negative. Serum bilirubin

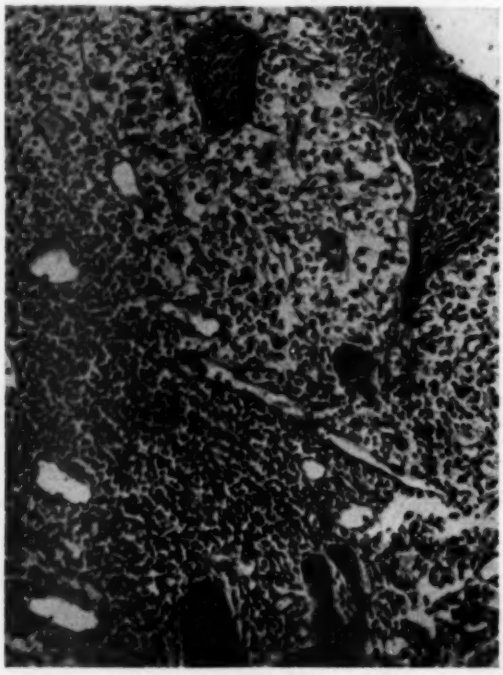

Fig. 3.—Compactly arranged infiltrate of gingival margin. Hematoxylin and eosin; × 130.

measured 15.7 mg. per 100 ml. total and 13.2 mg. per 100 ml. direct. Cephalin flocculation was 3 + in 24 hours and 4 + in 48 hours. Total serum proteins were 4.85 gm. per 100 cc., with 2.19 gm. per 100 cc. of albumin and 2.66 gm. per 100 cc. of globulin. The nonprotein nitrogen measured 24 mg. per 100 cc. Total serum cholesterol was 115 mg. per 100 cc. Alkaline phosphatase was 5.35 Bodansky units. Tuberculin, histoplasmin, and coccidioidin skin tests were negative. Two blood cultures showed a pseudomonas-like organism, but both cultures were considered to be contaminated. A completely satisfactory bone marrow biopsy specimen was difficult to obtain, but the general appearance indicated a left shift in all three series of cells. No abnormal cells were seen. Chest roentgenogram revealed the presence of a high diaphragm, probably due to the abdominal distention. The lungs showed a fine mottling in the inner zones which suggested bronchopneumonia or pulmonary congestion. Roentgenograms of the long bones, skull, ribs, and vertebrae disclosed no abnormalities. A roentgenogram of the mandible demonstrated no destructive lesions.

The course in the hospital was downhill. Therapy consisted of administration of penicillin, 300,000 units daily. The patient was given frequent small transfusions of whole blood alternated with infusions of salt-poor human serum albumin in 5% glucose in water. The edema of the extremities responded slightly to this therapy, but there was no improvement in the hematological findings. The highest hemoglobin and red cell counts reported were 7.6 gm. and 2,200,000 red cells, respectively. The patient ran a low-grade fever, the temperature varying from 100 to 101 F. during most of his hospitalization. Scant, stringy, loose stools, pale yellow in color, were noted throughout the hospitalization. New petechial lesions continued to appear over the upper extremi-

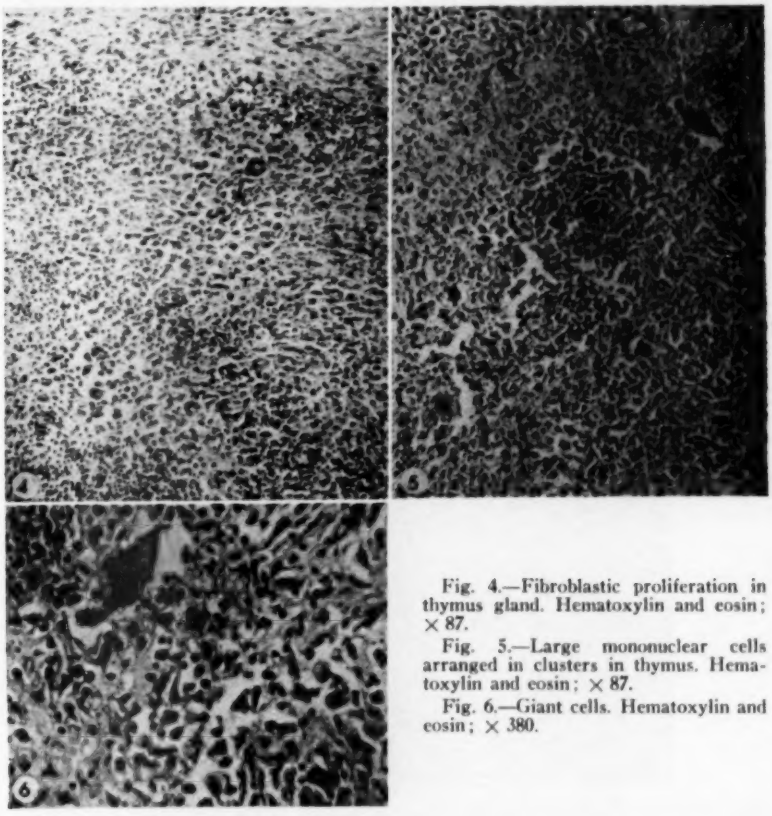

Fig. 4.—Fibroblastic proliferation in thymus gland. Hematoxylin and eosin; × 87.

Fig. 5.—Large mononuclear cells arranged in clusters in thymus. Hematoxylin and eosin; × 87.

Fig. 6.—Giant cells. Hematoxylin and eosin; × 380.

ties, chest, and abdomen. It was necessary to do paracenteses on the 5th and 16th days of hospitalization. Approximately 2,000 ml. of yellow fluid was removed on the first occasion and 1,225 ml. on the second. Bacteriological and pathological study of the ascitic fluid revealed no abnormalities. The patient became increasingly lethargic and died on the 17th day of hospitalization.

Autopsy Findings.—The external examination revealed findings as previously noted. The gingival margins were soft, hemorrhagic, and thickened. Microscopically, a dense infiltration of large mononuclear cells was present just beneath the mucosa (Fig. 3). There were numerous fibrous pleural adhesions bilaterally. The thymus was firmly adherent to the pericardium, firm in consistency, grayish-white in color, and 20 gm. in weight. Microscopic sections of the thymus showed only a few remaining areas of recognizable thymic tissue. The proliferating fibrous con-

nective tissue was well-demonstrated with Masson's trichrome stain (Figs. 4, 5, and 6). There were several large cells with acidophilic-staining cytoplasm, prominent and variably shaped nucleoli, and rather poorly defined cellular margins. A few large mononuclear cells with foamy cytoplasm were noted. When stained with Sudan IV stain according to the frozen section technique, some of these cells were found to contain small sudanotrophic vacuoles. A few phagocytized red blood cells were present within their cytoplasm. Many of the large mononuclear cells with foamy cytoplasm did not stain with the Sudan IV stain. Scattered clusters of lymphocytes were present throughout the section. The pericardium contained 10 ml. of yellow fluid. The heart weighed 60 gm. No pertinent pathological changes were noted in the sections of the myocardium. The right lung weighed 110 gm., while the left lung weighed 130 gm. The histo-

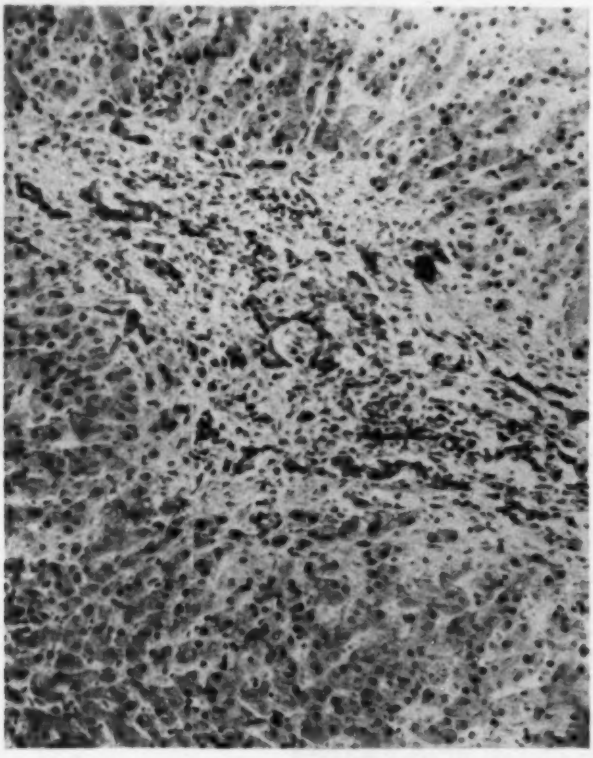

Fig. 7.—Fibrosis of portal areas of liver with bile duct proliferation. Hematoxylin and eosin; × 130.

logical sections showed some inflammatory infiltration about the bronchi. In the alveoli there were a few of the large mononuclear cells with foamy cytoplasm. Many of these cells contained phagocytized debris, erythrocytes, and vacuoles. Periodic-acid-stained sections of this tissue showed no specific etiological agent.

On opening of the abdominal cavity, approximately 500 ml. of clear, greenish-yellow fluid was noted. The liver extended 4 cm. below the costal margins in the right and left midclavicular lines and 6 cm. below the tip of the zyphoid process. A pinkish fluid, 500 ml., was present in the stomach. Peyer's patches of the ileum were prominent. The mesenteric lymph nodes measured 5 to 15 mm. in diameter and had a moist, grayish-pink cut surface. The liver weighed 800 gm. Numerous nodular projections were present on the capsular surface. A greenish-yellow color

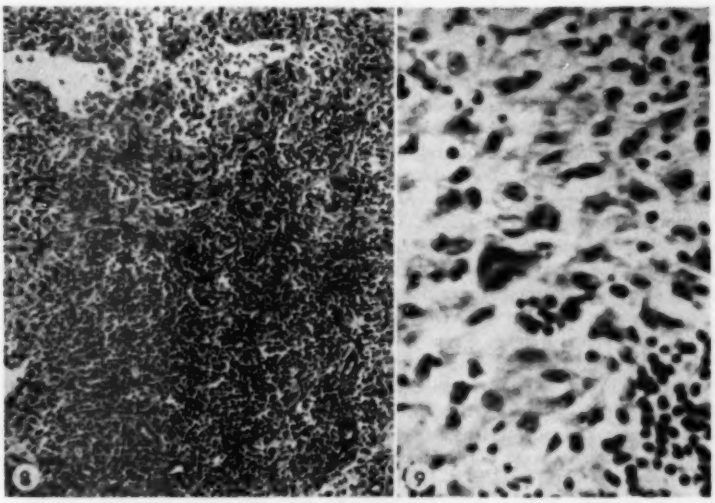

Fig. 8.—Distorted architectural features of lymph node. Hematoxylin and eosin; × 87.
Fig. 9.—Prominence of mononuclear cells with foamy cytoplasm. Hematoxylin and eosin; × 380.

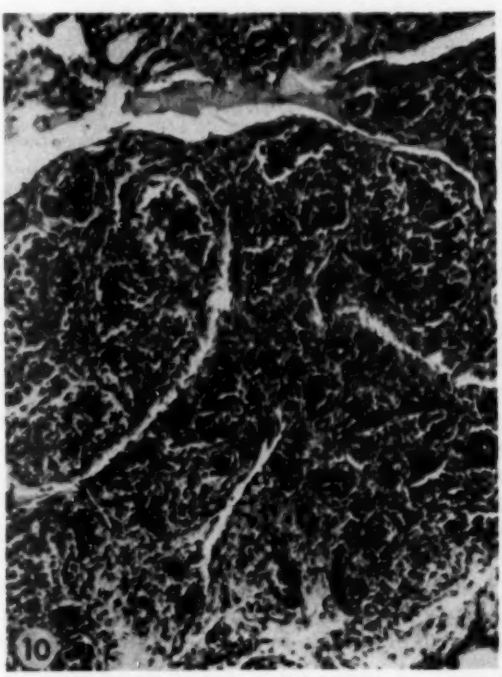

Fig. 10.—Fibrosis and infiltration of thyroid gland. Hematoxylin and eosin; × 130.

was noted upon sectioning, and the cut surface was firm in consistency. Microscopic preparations from several areas showed an increased amount of connective tissue in the portal spaces, bile duct proliferation, bile stasis, and an increase of lymphocytes and mononuclear cells in the portal spaces (Fig. 7). The Kupffer cells contained a brown pigment. Cut surfaces of the 250 gm. spleen were firm in consistency and presented a uniform bluish-purple color. Sections confirmed the gross impression of a fibrocongestive splenomegaly. The pancreas was firm but not otherwise remarkable. An increase in the intralobular and perilobular connective tissue and an increase in number of lymphocytes and mononuclear cells were the most conspicuous microscopic features. The adjacent pancreatic lymph node showed a considerable distortion of the normal architecture, although it was not completely destroyed. This variation was due to a proliferation of reticuloendothelial cells. Here again there were large mononuclear cells containing foamy cytoplasm and phagocytized red blood cells and debris (Figs. 8 and 9). Only an occasional large mononuclear cell contained sudanotrophic material. There was a small area of fat necrosis at the margin of one section. Sections of several mesenteric lymph nodes showed a less distorted nodal architecture. The kidneys weighed 60 gm. each. The smooth brown cortical surface was separated from the capsule with ease. The cortical and medullary areas were well defined. Sections of the kidney showed bile casts in the convoluted tubules and in the collecting tubules. At other points, the tubular epithelium was characterized by parenchymatous degeneration. The thyroid presented no gross pathological changes; in the histological sections there was an increase in the fibrous connective tissue which caused a considerable variation in the normal architecture. The acini were distorted. Focal collections of lymphocytes and mononuclear cells were noted throughout the sections of the thyroid (Fig. 10). The majority of these mononuclear cells did not contain material that stained with Sudan IV. Parathyroid glands showed no pathological changes. The bone marrow exhibited a moderate erythroid hyperplasia.

CHEMICAL STUDIES OF TISSUES†

Data for total cholesterol, cholesterol esters, phospholipids, and total fat from sections of spleen and liver were comparable to those for a control. These data will be discussed under "Comment."

COMMENT

The classic diagnostic features of nonlipoid reticuloendotheliosis outlined by Siwe in 1933 [8] consisted of (1) its character as a nonfamilial disease of unknown etiology, usually occurring in infancy or early childhood and ending fatally after an illness of a few weeks' to several months' duration; (2) moderate to marked enlargement of liver and spleen; (3) moderately enlarged, discrete, nontender lymph nodes; (4) a hemorrhagic diathesis consisting chiefly of petechial skin lesions; (5) a progressive hypochromic anemia; (6) a low-grade temperature elevation; (7) production of localized bone defects in some cases; (8) a generalized hyperplasia of the reticuloendothelial system involving the spleen, liver, lymph nodes, skin, bone marrow, and thymus gland.

The typical features with the exception of the localized bone defects were observed in this case. In addition, two unusual findings were noted; namely, jaundice, with laboratory evidence of severe liver injury, and generalized edema.

Although some cases of Letterer-Siwe's disease have an acute onset, this patient's illness began typically with vague complaints of malaise, irritability, and anorexia. A bleeding tendency is also often an early complaint. The petechial skin lesions are usually most severe in areas of greatest friction, such as the neck, groins, and axilla. A greasy, scaly seborrheic-like dermatitis most prominent on the scalp has been occasionally described and was severe on the scalp as well as upper chest of this patient.

† Chemical analyses were performed by Dr. Hilda F. Wiese, Department of Pediatrics.

Cystic destructive lesions, commonly involving flat bones, are often observed roentgenographically. The only suggestion of bone involvement in this patient was loosening of the teeth. A diffuse increase of the perihilar lung markings due to infiltration of the granulomatous process has been occasionally reported on chest x-ray examination. A similar finding was noted in this patient.

Reported instances of disturbed liver function are rare. Two cases of Letterer-Siwe's disease with jaundice have been recorded. The first was seen at the Massachusetts General Hospital,[9] and the second was a case of Wallgren in which there developed jaundice, bile in the urine, and clay-colored stools (this was thought to represent an infectious hepatitis). In the latter case there was no reticuloendothelial proliferation or infiltration of foam cells in the liver. The patient described in the present report showed evidence of moderately severe jaundice with laboratory evidence of liver damage including markedly positive cephalin flocculation, lowered prothrombin time, reduction in serum proteins, and reversal of the albumin-globulin ratio. Since the hepatic fibrosis was occasionally associated with infiltration of the portal areas by large atypical mononuclear cells and lymphocytes similar to those observed in the thymus, lymph nodes, and other viscera, it may be postulated that these fibrotic changes were sequelae of hepatic involvement in this disease. A review of the literature would indicate that this has been an infrequent postmortem finding. The similarity of these hepatic lesions to the changes noted in the other organs is striking. The collections of large mononuclear cells in the regions of the portal triads suggest that these were sites of more severe reaction which resulted in fibrosis. Similar focal and diffuse fibrotic changes were observed in other organs. The congestive splenomegaly can then be accounted for on the basis of portal hypertension. Additional cases may add valuable information as to the exact pathogenesis of the hepatic lesions in Letterer-Siwe's disease. The possibility of deficiencies in the diet contributing to the liver damage could not be definitely excluded in this case and therefore might have been a contributing factor to the hepatic involvement.

Edema and ascites, as noted in this patient, were reported by Harvard[10] for the first time. These findings in the present case may properly be attributed to the hepatic fibrosis, with reduced serum proteins, and to the anemia.

The extremely low platelet count of 16,560 per cubic millimeter in this patient is deserving of comment, since thrombopenia, if present, is usually slight or moderate. Harvard's patient had a thrombocyte count of 12,500 per cubic millimeter, the lowest so far reported.

Pathologically, the infiltration of various organs by the large atypical foam cells without lipoid deposit has also been observed in early granulomatous lesions in the Hand-Schüller-Christian syndrome. It is on this basis that Wallgren, Farber, and other investigators contend that Letterer-Siwe's disease is a more malignant variant of the same pathologic process, from which the patient dies before lipid cellular changes are marked. More recently Lichtenstein[11] has pointed out the similarity and variability of the pathological changes in tissues involved in Letterer-Siwe's disease, Schüller-Christian disease, and eosinophilic granuloma of bone. Because of these manifestations, which suggest that the diseases are variations of one entity, the name "histocytosis X" has been suggested. Many of the features

observed in this case would lend support to this concept; however, we feel that it is important to differentiate Letterer-Siwe's disease because of the difference in prognosis and therapy.

The chemical analysis of the liver and spleen in this patient revealed the values for various lipids to be the same as those for the normal control. This observation would seem to be in agreement with the nonlipoid characteristics of this disease described histologically.

SUMMARY

A case of Letterer-Siwe's disease, with the unusual findings of severe liver disease and generalized edema was observed in a 2½-year-old boy. The clinical features and histopathology of the lesions in the gingiva, thymus, lungs, liver, lymph nodes, and thyroid gland have been described. References are made to previous articles which have pointed out that Letterer-Siwe's disease is variant of the process which includes Hand-Schüller-Christian disease and eosinophilic granuloma.

Chemical studies of various involved tissues are reported for the first time. The values obtained are in agreement with the nonlipoid nature of this disease.

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COLLOIDOPHAGY IN THE THYROID GLAND

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A PAPER on colloidophagy was presented by Tanabe and Wakabayashi [1] in 1940 before the Society of Japanese Pathologists. These authors observed in the colloid of normal thyroids cells which had the appearance of monocytes. The Japanese investigators were the first to use the term "colloidophagy." In 1943 Buño [2] described colloidophagy in chronic thyroiditis and illustrated this process with beautiful photomicrographs. My first paper [3] on colloidophagy was published without knowledge of these two papers, which appeared in Japanese and Spanish publications.

MATERIAL AND METHODS

The present paper is based on the histologic study of 548 thyroids obtained by autopsy and 75 goiters removed at operation. Paraffin sections were stained with hematoxylin and eosin, Mallory's aniline blue method, cresyl violet, the periodic acid-Schiff stain, and Sudan black B (Baker).

RESULTS

In 88 of 548 thyroids obtained by autopsy, macrophages were present in thyroid follicles. They were absent in patients under the age of 20, rare in the third decade of life, and frequent after the age of 50. The total relative frequency in our material, i. e., 16.2%, compares well with the figures of the Japanese authors (16%); however, they found most of their positive cases in the age group of 21 to 40 years, and found them twice as frequently in males as in females, while in our material women over 50 years of age predominated. Tanabe and his co-workers believed that chronic wasting diseases predisposed to colloidophagy, while I did not find any relationship between cause of death and occurrence of this phenomenon. The Japanese investigators did not mention the association of colloidophagy and aggregation of lymphocytes adjacent to the involved thyroid follicles, which was almost always present in my material.

Of 75 surgical goiters which I studied, 49 showed the presence of macrophages containing colloid. I found them not only within thyroid follicles, but also in the follicle wall, in groups of lymphocytes, or in the lymph follicles. They were most frequent in exophthalmic goiter and chronic thyroiditis.

COMMENT

Loeb and Basset [4] (1930) were the first who described macrophages in thyroid follicles of animals and who believed that colloid resorption by phagocytes plays a significant part in the normal removal of colloid. Thurston [5] saw stimulation of the process by injection of pituitary extract in guinea pigs, cats, pigions, and rats.

From the Hertzler Research Foundation.

Eggert [6] saw in lizards, after injection of thyrotropic hormone, wandering cells enter the hyperactive follicles, ingest colloid, and carry it into blood vessels. Williams [7] implanted thyroid tissue in transparent chambers into rabbit ears and observed in the living tissue macrophages entering follicles. Thyrotropic hormone increased the activity of these colloidophages. There was no evidence of degeneration of the epithelial wall of the invaded follicles. Williams believed that some special chemical alteration of the colloid stimulates the entry of macrophages into thyroid follicles but did not suggest the nature of this chemotactic substance. Several observations suggest that thyrotropic hormone increases the content of the thyroid in phospholipid. Morton and Schwartz [8] demonstrated in vitro that phospholipid is increased markedly in supravital thyroid tissue after adding thyrotropin. Dobyns [9] found a large number of lipid droplets in the thyroid epithelium of guinea pigs after injection of thyrotropin (Antuitrin T). Ferguson [10] injected subcutaneously lipid extracts from thyroid colloid into guinea pigs and saw histiocytes, giant cells, and lymphocytes attracted by the injected lipid. In the colloid and interfollicular tissue of our positive cases macrophages were found, with granules which stained black with Sudan black B.

SUMMARY

In 16.2% of thyroids obtained by autopsy, macrophages were found in the lumen of follicles. The involved follicles were surrounded by lymphocytes. There was no relationship between presence of colloidophages and cause of death. Women older than 50 years predominated in our positive cases.

In 49 of 75 surgical goiters, colloidophages were noticed. They were present not only within the follicle lumen, but also in the follicle wall, in the center of lymph follicles, and in the interfollicular tissue.

Exophthamic goiters and thyroids with chronic thyroiditis were most frequently represented in our positive findings.

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POLYKARYOTIC HEPATITIS IN A PATIENT TREATED WITH PARAAMINOSALICYLIC ACID

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AND
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THE FOLLOWING case is reported because of the extraordinary appearance of the hepatic cell nuclei and its possible relation to chemotherapy.

REPORT OF A CASE

A 56-year-old man had far-advanced bilateral pulmonary tuberculosis, of 13 year's duration, and had had bilateral renal tuberculosis during the last year, as diagnosed clinically, roentgenologically, and by multiple examinations positive for Mycobacterium tuberculosis. For the last two years he had received streptomycin, *p*-aminosalicylic acid, sulfonamides, and penicillin.

Blood counts revealed 4,320,000 to 4,950,000 erythrocytes, 9,700 to 13,300 leucocytes, 13 to 16% staff cells, and 2 to 5% eosinophiles; the differential leucocyte count was otherwise normal. Serum potassium on the day of death was 16.5 mg. per 100 cc.

Autopsy was performed 1 hour 45 minutes after death. Gross diagnoses were fibrocaseous tuberculosis of lungs with multiple cavities in all lobes; bullous emphysema; empyema of right pleura; caseous tuberculosis of kidneys, prostate, and mesenteric lymph nodes; peptic ulcer of first portion of duodenum, and atherosclerosis, moderate, of right coronary artery and abdominal aorta. The liver weighed 1,051 gm. It was smooth, reddish-brown, and slightly indurated. The cut surface was smooth. Lobular markings were prominent. The extrahepatic bile tract was patent and contained thin green bile. Microscopic examination confirmed the gross diagnoses.

Histology of the Liver.—Scattered throughout the lobules were many large hepatic cells containing multiple or multilobar nuclei. Multiple nuclei were the predominant type, associated in various proportions with lobes connected by narrow zones of nuclear substance. The two types sometimes coexisted in one cell. For the sake of brevity both will be designated as polykaryotic. Glycogenic vesiculous nuclei were numerous and large, contrasting with nonglycogenic, often hyperchromatic, nuclei in the same cell. Nucleoli were large, and varied from one to four per nucleus or lobe. One syncytium contained a cruciate figure suggestive of a tetrapolar mitosis. This was the only mitosis seen. The number of nuclei or lobes varied up to 40 per

From the Veterans Administration Area Reference Laboratory, Veterans Administration Hospital, Bronx, N. Y., and the Laboratory Service of the Veterans Administration Hospital, Castle Point, N. Y.

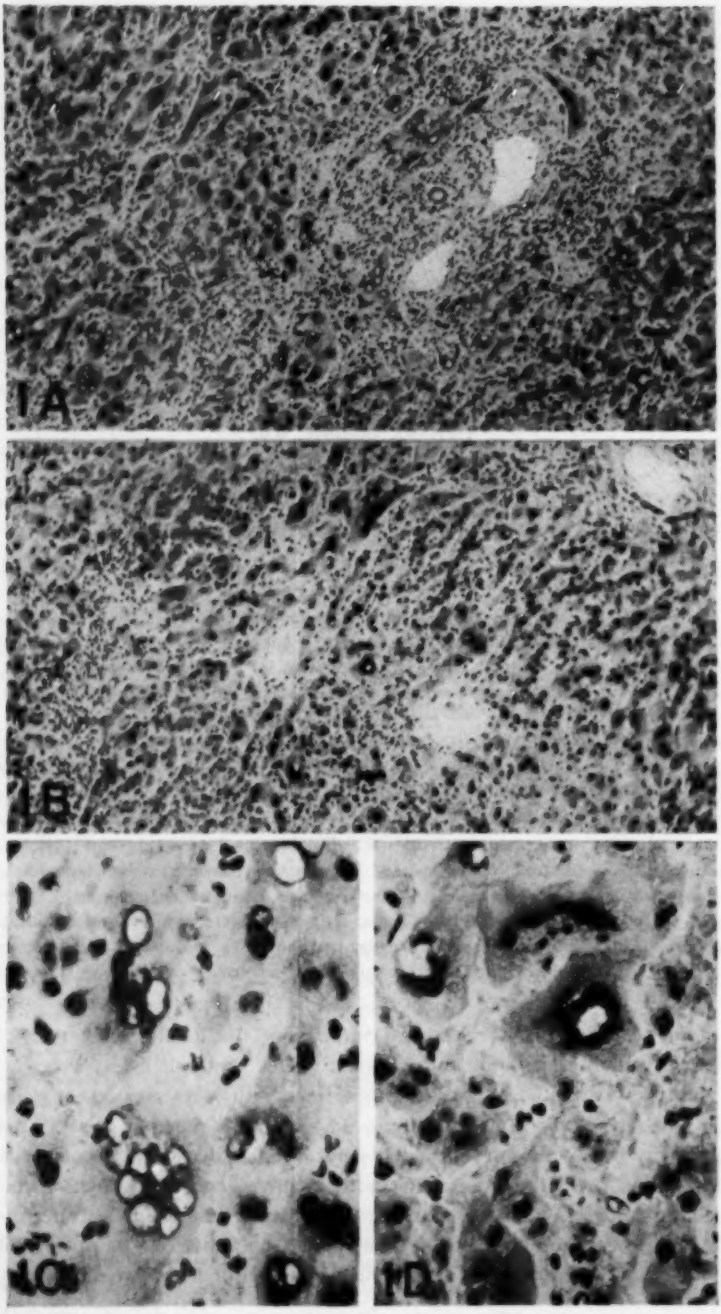

Fig. 1.—*A*, area about a portal space, showing numerous multinucleate hepatic cells, many glycogenic nuclei, scattered leucocytic infiltrate; × 85. *B*, area about centrolobular veins; × 85. *C* and *D*, details of *A* and *B*; nuclear rosette about fat droplets in *D*; × 416.

cell. Their frequency distribution among 1,000 unselected hepatic cells is shown below. N signifies the number of lobes or nuclei, and C the number of cells in each class.

N	0	1	2	3	4	5	6	7	8	9	10	11-13	14	15-17	18	19-22	23
C	166	585	129	59	27	7	8	6	3	4	3	0	1	0	1	0	1

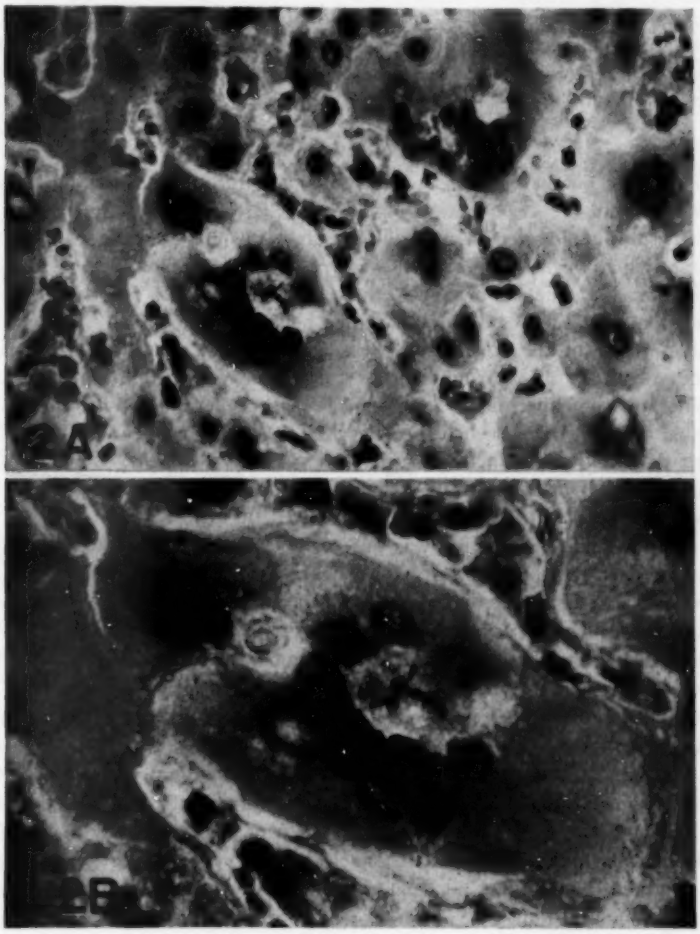

Fig. 2.—*A*, multinucleate cells, including one with cruciate structure suggesting multipolar mitosis; × 416. *B*, detail of *A*; the two giant cells enclose a sinusoid containing an erythrocyte; × 775.

The zero class is due to the cutting off of anuclear cell portions by the microtome. The nuclei were usually central, forming a dense cluster or a rosette.

Small lipid droplets and fine pigment granules were scattered in the cytoplasm of uninucleate and polykaryotic cells. Rare granules were shown by acid ferrocyanide to be hemosiderin. Others, with shades of green and brown, were inter-

preted as bile and lipochrome. None gave the acid-fast reaction of ceroid. No acid-fast bacilli were found in the liver. Glycogen was demonstrated with periodic acid-leucofuchsin controlled with amylase in the cytoplasm of many hepatic cells and in the vesiculous nuclei. Portal spaces were frequently widened by fibrosis and by infiltration with lymphocytes, macrophages, neutrophiles, and eosinophiles. Small bands of infiltration extended into the lobules. Within lobules there were small neutrophilic collections. A reticulum stain showed a generally normal intralobular lattice, but occasional small patches were densified without thickening of the fibers, suggesting that the meshes had collapsed after destruction of the contained cells. No tuberculous lesions were seen in the liver.

COMMENT

The hepatic polykaryosis is qualitatively no different from that often seen in conditions leading to regeneration of hepatic cells. But quantitatively it is of an extremely unusual degree in an adult. Postmortem increase in the numbers of binucleate hepatic cells of the rabbit was reported by Reinke [1] and Münzer.[2] In the present case the degree of polykaryosis, far exceeding any reported postmortem phenomenon, and the coexistence of other hepatic lesions justify the conclusion that all or most of the polykaryosis was ante mortem. Hypotheses of origin of hepatic syncytia by fusion, amitosis, or mitosis have been extensively discussed in the literature on experimental liver damage and regeneration. Wilson and Leduc * concluded that all three mechanisms may be at work. Herxheimer and Thölldte [5] believed that in the human liver, regenerating syncytia arise by both mitosis and amitosis, the latter being the more frequent, whereas Pfuhl [6] maintained that apparently amitotic binucleate cells might be produced by fusion.

In our case only one mitosis was observed. Its pattern suggested tetrapolarity, and it occurred in a polykaryotic cell. The rarity of mitoses cannot rule out an antecedent wave of mitoses as the origin of the polykaryocytes. The presence of a tetrapolar mitosis in a non-neoplastic human hepatic cell is noteworthy. In the mouse liver, following various noxae, Wilson and Leduc [3] observed multipolar mitoses, which they interpreted as occurring in multinuclear cells. Thus, multipolar mitosis would be the result, not the cause, of multinuclearity. Several authors have suggested that hepatic syncytia may be polyploid.† However, Wilson and Leduc [3] have pointed out the difficulty of counting chromosomes accurately, even in dividing liver cells. Fankhauser and Humphrey [11] proposed the use of the number of nucleoli, and Beatty,[12] the nucleolar mass as a measure of ploidy in nondividing cells. But the former pointed out that nucleolar fusion might obscure the relation, and Lagerstedt [13] found the nucleoli in the liver reduced by a protein-poor diet. In view of the questionable value of such determinations, no conclusion can be drawn as to ploidy of the polykaryotic cells in the present case.

Giant hepatic cells with as many as 40 nuclei were found by Binder,[14] Lonicer,[15] and Gruber [16] in congenital syphilis, and such cells with 20 nuclei, by Craig and Landing [10] in neonatal hepatitis. In both studies, the syncytia were elongated in the direction of hepatic cords, a feature differing from the present picture. Gall ‡

* References 3 and 4.

† References 3 and 7 through 10.

‡ Gall, E. A.: Personal communication to the authors.

attributed the frequency of multinuclear cells in necrotizing infantile liver disease to the growth potential in children. In adult epidemic hepatitis, Lucké [17] observed syncytia having mostly from two to six nuclei. The largest number shown was 19.

In the present case there was no definite clue to etiology. Leucocytic infiltration and evidence of past hepatic cell destruction suggest subacute hepatitis. The presence of eosinophiles does not contribute to the diagnosis. These cells are sometimes seen in viral hepatitis.[18] A hepatotropic virus or a toxic or an allergic effect of any of the drugs used may have been the cause. Apparently, streptomycin has not been known to damage the liver.[19] Clinical hepatitis has been interpreted as an effect of *p*-aminosalicylic acid (PAS).§ Histologic studies have been reported in two cases. In one case Efskind [23] described acute necrotic hepatitis, but the patient had received several other drugs and had agranulocytosis and thrombocytopenia. Allen, Beacham, and Keschner [19] suggested that hypokalemia secondary to PAS might be a factor in producing hepatitis, but their case was complicated by miliary tuberculosis of the liver. In neither case were the lesions of the type reported here. Thus, no clear histologic picture of unequivocal PAS hepatitis has yet emerged, although clinically there is some evidence that the entity may exist. In the present case, the patient received PAS but had no recorded clinical manifestation of hepatitis. The one serum potassium determination was performed on the day of death, and its result was normal. There was no myocardial lesion, such as might have occurred in hypokalemia. Hence no conclusion can be drawn as to the role of PAS. It is suggested that future cases of histologically studied hepatitis in PAS-treated patients be reported with a view to ascertaining whether a distinctive lesion occurs.

SUMMARY

At the autopsy on a patient with far-advanced pulmonary tuberculosis who had received *p*-aminosalicylic acid and other drugs, the liver was found to have an extraordinary degree of multiplicity and multilobarity of nuclei in hepatic cells, associated with leucocytic infiltration, focal necrosis, and other evidence of hepatitis. The infiltrate included many eosinophiles. Clinically, no evidence of liver disease had been observed. The possibility that the liver lesion may be the morphologic aspect of a clinically inapparent hepatitis secondary to use of *p*-aminosalicylic acid is considered.

Dr. Benjamin S. Gordon made available to one of us (A. F. L.) the sections in this case.

Mrs. Alicia G. Liber assisted in collecting and evaluating references.

Messrs. Eli Traub and Ralph Maiello performed special staining techniques.

Messrs. Sidney Shapiro and Masi M. Nakamura made the photomicrographs.

§ References 20 through 22.

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HISTOLOGIC STUDY OF THE BONE MARROW IN NORMAL WHITE PEKIN DUCKS

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THE INCREASING use of ducks as experimental animals necessitates a thorough knowledge of their hematological status. Much work has been done on the anemias produced by protozoan infections and by various chemical agents, but very few factual data are available on the normal values of the bone marrow in the white Pekin duck.

Magath and Higgins,[1] in 1933, tabulated facts on the peripheral blood of ducks but made no mention of their marrow cells. Hewitt,[2] in 1942, found that there was considerable disagreement among investigators regarding the terminology and characteristic appearance of white cells in birds. He referred to parent cells in bone marrow but gave no descriptions or tabulations of these cells. Rigdon and Rostorfer,[3] in 1947, discussed some aspects of the erythroid cells in marrow but did not give a differential marrow picture.

MATERIAL AND METHODS

The bone marrow from 50 normal white Pekin ducks was examined in order to determine the distribution of the various cellular constituents. These ducks were maintained on Purina Duck Startena and Growena and cracked corn and kept either in batteries in the laboratory or in outside open pens. They ranged in age from 3 to 90 days.

Beginning with ducks 3 days old, one to three birds were killed daily during a period of four weeks. Thereafter, they were killed at five-day intervals for the following three months. Each duck was killed by severing the carotid artery, thus producing rapid exsanguination. The marrow was immediately aspirated, smeared on glass slides, and stained at once, using aged Wright's stain, and counterstained with Giemsa stain, buffered at pH 6.8. The correct pH of the buffer is absolutely essential if the granules of the eosinophiles and heterophiles are to be well differentiated. Duck bone marrow requires a longer staining period than mammalian marrow. Two hours is required for satisfactory preparations. Slides were placed in a refrigerator while staining to avoid the precipitation of the stain that occurs when slides are exposed for this length of time at room temperature in this climate.

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In order to assure representative sampling, smears of bone marrow were taken from the tibia, femur, and humerus of each duck. These bones were cut through the center and marrow was aspirated with a sternal puncture needle. As the birds grew, marrow became more difficult to aspirate, since the cells were being replaced by fatty and fibrous tissue. In ducks less than 21 days of age active marrow could be found in all parts of the bones examined. After 30 days marrow was most active in the humerus. In ducks over 40 days of age all the bones showed fatty invasion with scattered areas of hematopoiesis. It was found that at this age smears made by the imprint method were superior to those made by aspiration.

A total of 1,000 cells was counted on each duck. Two hundred fifty cells were counted on each smear from the humerus and femur and from both of the smears made from the tibia. The diameters of the cells of the bone marrow were measured on a micrometer scale.

Supravital stains were made as an adjunct for studying the granules of the myeloid series.

DESCRIPTION OF CELLS

A. Erythroid Series.—Since the red cells in the duck are nucleated, the use of the term normoblast in tabulation of cells in the marrow is eliminated. The differentiation between the erythroblasts and the circulating red cells must be based on polychromasia of the cytoplasm and pyknosis of the nucleus. No cells were included in the erythroblast class unless there was a gray cytoplasm and the chromatin of the nucleus had a spoke-wheel pattern.

1. The proerythroblast is a large cell, 10 to 15 μ in diameter, having a large purple nucleus 8 to 9 μ in size. The nucleus is a loose chromatin structure and occupies the center of the cell. The narrow rim of cytoplasm routinely stains deeply basophilic; however, sometimes it stains greenish-blue in color. There are four to six dark parachromatin bodies overlying the nucleus. In supravital preparations the nucleus and cytoplasm do not stain; only a few green mitochondria may be seen scattered throughout the cytoplasm.

2. The erythroblast averages 8 to 10 μ in diameter and has a large, round centrally placed nucleus with a narrow rim of dark-gray- to bluish-gray-staining cytoplasm. The nuclear chromatin is denser than that in the proerythroblast, and in many cells it assumes a spoke-wheel arrangement. Four to six parachromatin bodies overlie the nucleus. In supravital stain, the erythroblast resembles the proerythroblast except for the smaller size and the increase in mitochondria.

3. The polychromatic erythroblast varies in size from 7.5 to 9 μ. The nucleus is dense but retains the radial arrangement of chromatin. Mitotic figures are most numerous at this level. Supravital study reveals the nucleus to have a pale green cast and a moderate number of mitochondria.

B. Myeloid Series.—1. The myeloblast ranges in size from 9.5 to 11.5 μ. It has a larger nucleus, of delicate chromatin network and six to eight nucleoli. The cytoplasm stains light gray around the nucleus, becoming a darker blue toward the periphery, thus forming a perinuclear halo. Frequently the cytoplasm of the myeloblast has knob-like projections, and they may help to differentiate the myeloblast from the proerythroblast. There are no granules in the myeloblast, but some cells have a condensation of the chromatin about the nucleoli. These cells have ameboid movement in supravital studies, but do not take the supravital dyes.

2. The promyelocyte is 10 to 12 μ in size, with a large nucleus of fine chromatin structure and several nucleoli. The cytoplasm stains blue and there are a few granules scattered throughout the cytoplasm; some granules overlie the nucleus. The majority of the granules are small, though a few large ones are present; they are reddish-purple and orange in color in a Wright's stain.

3. The heterophile myelocyte is a large cell 12 to 15 μ in diameter. A centrally placed nucleus is surrounded by pale blue-staining cytoplasm, which may show areas of pink, depending on the age. The older cells show an increase in the amount of pink cytoplasm. The granules, which frequently overlie the nucleus, are of two types: large reddish-purple granules, and light orange-staining granules, both of which are round. In supravital stain, the majority of the granules have a yellowish-green tint, a few are dark red, and some are orange in color.

4. The heterophile metamyelocyte is 12 to 14 μ in diameter. The nucleus is pushed to one side and may or may not be indented along one edge. A few cells retain a nucleolus. There is a wide, pale pink cytoplasm with a few remaining small blue areas. The cytoplasm is filled with granules, the majority of which stain light

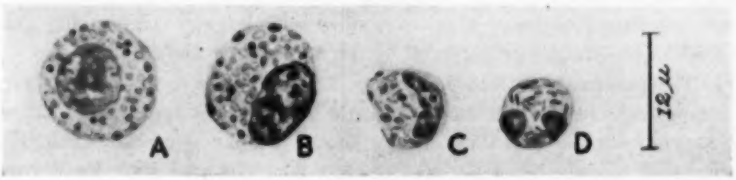

Fig. 1.—The gradual change in the shape of the granules can be followed from the myelocyte to the mature heterophile. The myelocyte shows only the round granules; the metamyelocyte contains both round and oval granules, the band heterophiles have ovoid and elliptical granules, and the segmented heterophiles contain only elliptical granules. *A*, heterophile myelocyte, round granules; *B*, heterophile metamyelocyte, round and oval granules; *C*, heterophile band cell, oval and elliptical granules; *D*, heterophile mature cell, elliptical granules.

orange to yellow in color. The granules at this stage are both round and oval. In supravital studies, heterophile metamyelocytes have active ameboid movement; some granules stain orange, but many show only a pale yellow color.

5. The heteroplile band cell has a nucleus of irregularly clumped chromatin, in the typical band shape, and contains numerous granules of a dull yellow and orange color. These granules are oval and elliptical in shape.

6. The segmented heterophile has a compact, multiple-lobed nucleus and a pale pink cytoplasm filled with elliptical, dull-yellow and orange-staining granules. In supravital stain these granules are elliptical and take only a pale yellow-green color. On standing from 20 to 30 minutes, one or two orange-colored vacuoles may develop in the cytoplasm.

These cells have been classified in peripheral blood by other workers as "polymorphonuclear cells with eosinophilic rods."[4] With well-controlled staining technique these granules can be shown to differ in color from the true eosinophile. Since these cells can be traced by the shape and staining reaction of their granules to the parent cell, the heterophile myelocyte, in our opinion these granulocytes should be classed as heterophiles in the peripheral blood. Apparently, the granules change from round to oval and then to elliptical during the process of maturation of the cell (Fig. 1).

7. The eosinophile myelocyte is 11 to 13 μ in size. The nucleus is frequently hidden by the dense accumulation of bright pink and brilliant orange-staining granules. These granules are highly refractile.

8. The eosinophile metamyelocyte is 9 to 11 μ in diameter. The nucleus is pushed to one side; the cytoplasm stains blue and is filled with refractile, pink-staining granules. These granules are predominately round, but some are bacillary in shape.

9. The eosinophile band cell has the typical band-shaped nucleus. The blue cytoplasm is filled with red, refractile, bacillary-shaped granules. Because of their high refractility, these granules appear to "twinkle" when brought into focus. The nucleus of these eosinophilic cells stains a deeper purple color than the nucleus of the heterophiles. These eosinophilic cells are referred to in other fowls as "eosinophiles with little spindle-shaped bodies," [4] and "true eosinophiles." [5] It is our opinion that because these cells differ in the staining of their nucleus and granules and in their origin, they should be considered as belonging to a separate group from the heterophiles.

10. The basophile myelocyte is a rare cell in duck bone marrow. Out of the total 50,000 cells tabulated, only 14 basophilic myelocytes were encountered. They had a clear, colorless cytoplasm, which was filled with large purple-staining granules. The nucleus was frequently obscured by the numerous granules.

11. The plasma cell is 7 to 9 μ in size. The nucleus is eccentrically placed, and the arrangement of the chromatin gives the spoke-wheel appearance. There is a wide zone of cytoplasm that stains deeply basophilic and may contain small vacuoles; the cytoplasm usually has a perinuclear clear zone. In vital stain there are many mitochondria.

12. The macrophage is 8 to 10 μ in size. It has a dark purple-staining nucleus, which is pyknotic and usually eccentric in position. The cytoplasm stains blue and is completely filled with small vacuoles.

13. The megakaryocyte is exceedingly large, measuring from 75 to 150 μ in its greatest diameter, and shows a clumping of the chromatin. The cytoplasm stains blue with pale-staining azurophilic granulations. There are 6 to 10 separate round to oval nuclei in each megakaryocyte.

14. The lymphocyte is approximately 6.5 μ in diameter. In the bone-marrow preparations these cells occur either in clumps or in islands. They may be confused with the platelets unless the preparation is thin, so that the cells are spread in an even distribution. The nucleus of the lymphocyte is frequently indented; the chromatin is clumped in four to six dense masses, whereas the nucleus of the platelet is more pyknotic. In supravital studies, lymphocytes are easily recognized by their mitochondria.

TABULATION OF CELLS

The differential counts of cells in the bone marrows are tabulated in Tables 1, 2, and 3 to show the variations with the increasing age of the ducks. The alterations in the erythrocytic-myelocytic ratio are represented graphically in Figure 2. The data in Tables 1 and 2 are from ducks 2 weeks of age and younger. The marrow is more active during this period than at any other time in the life of the duck. Table 3 shows the type of cells in the marrow of birds during the second and third months. Only slight changes occur in the bone marrow during this age.

TABLE 1.—*Marrow Cells in 3 to 15-Day-Old Ducks*

	Experimental Days											
	3	4	5	6	7	8	9	10	12	13	14	15
	Number of Ducks in Each Experiment											
	1	1	2	1	2	1	1	2	1	1	3	2
Proerythroblast	8.0	9.0	7.6	7.0	6.2	7.0	7.2	6.0	6.0	5.0	3.6	3.6
Erythroblast	15.2	14.0	14.0	13.6	13.8	13.5	12.6	17.4	16.8	14.6	13.6	16.0
Polychromatic erythroblast	44.8	43.8	43.4	44.6	44.6	44.0	45.0	40.0	39.5	41.2	42.0	38.2
Myeloblast	0.6	1.0	0.6	0.4	0.6	0.6	0.4	0.4	0.8	0.6	0.8	0.4
Eosinophile myelocyte	1.8	2.0	1.6	2.0	1.6	1.8	1.8	3.2	3.8	3.0	2.4	1.0
Eosinophile metamyelocyte	4.4	3.7	4.6	4.6	4.8	4.8	3.6	5.4	4.4	4.8	6.0	3.0
Eosinophile, band	1.0	1.5	1.4	1.8	1.8	2.0	2.2	1.0	1.4	1.4	1.6	2.4
Eosinophile, segmented	1.4	1.8	1.4	2.4	2.2	2.0	3.0	2.4	2.2	1.8	1.6	3.2
Heterophile myelocyte	4.2	4.0	3.4	4.2	3.4	3.6	2.4	2.0	1.6	1.4	2.8	4.0
Heterophile metamyelocyte	5.6	5.8	6.0	6.2	5.6	5.8	7.6	6.4	8.4	8.6	8.6	8.0
Heterophile, band	1.0	1.5	1.4	1.8	1.8	2.0	2.2	1.0	1.4	1.4	1.6	2.4
Heterophile, segmented	8.0	8.4	9.2	7.0	8.4	8.0	6.8	9.0	8.6	10.6	9.0	10.8
Lymphocyte	1.0	0.8	0.8	1.6	0.8	0.8	1.4	1.0	0.8	0.4	1.2	0.8
Monocyte	0.2	0.2	0.4	0.2	0.2	0.2	0.2	0.2	0.4	0.4	0.4	0.4
Plasma cell	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.4	0.2	0.4
Megakaryocyte	0.4	0.8	0.4	1.2	1.2	0.8	1.4	0.8	1.0	0.8	1.6	1.6

TABLE 2.—*Marrow Cells in 16 to 30-Day-Old Ducks*

	Experimental Days											
	16	17	19	20	21	22	24	25	26	27	28	30
	Number of Ducks in Each Experiment											
	3	2	2	3	3	2	2	2	3	2	1	2
Proerythroblast	3.6	4.0	3.0	2.7	3.9	3.0	3.0	2.6	2.0	1.0	1.8	2.0
Erythroblast	17.0	18.5	11.9	10.6	17.6	11.2	13.0	13.8	14.5	12.1	13.0	13.5
Polychromatic erythroblast	32.4	31.3	38.0	39.0	27.8	36.2	30.0	31.0	28.5	31.0	28.2	27.0
Myeloblast	0.4	0.6	0.8	0.8	0.2	1.0	0.6	0.4	0.4	0.4	1.0	1.2
Eosinophile metamyelocyte	2.6	2.4	3.4	2.8	3.0	2.2	2.2	1.8	2.0	1.8	2.8	3.6
Eosinophile, band	2.4	1.6	3.2	1.8	3.0	1.6	1.4	1.8	0.6	0.8	2.8	3.6
Eosinophile, segmented	3.4	3.0	3.8	5.4	5.2	3.4	2.0	1.4	1.4	1.4	3.0	3.2
Heterophile myelocyte	3.4	2.8	2.0	1.6	1.0	3.0	3.8	3.0	2.4	2.0	2.0	2.0
Heterophile metamyelocyte	10.7	9.6	9.4	9.2	7.7	10.4	10.4	11.2	11.4	11.6	10.6	11.0
Heterophile, band	7.4	8.2	6.0	8.0	9.6	9.0	12.8	12.0	12.8	13.2	12.0	8.8
Heterophile, segmented	12.4	13.0	13.2	13.0	15.8	15.0	19.0	20.0	20.2	23.8	18.4	18.8
Lymphocyte	1.6	1.0	1.4	1.2	1.2	0.8	1.4	0.8	1.0	0.6	0.8	1.2
Monocyte	0.6	0.6	0.6	0.8	0.8	0.4	0.8	0.4	0.4	0.2	0.4	0.4
Plasma cell	0.4	0.4	0.6	0.8	1.0	0.4	0.6	0.2	0.2	0.2	0.4	1.2
Megakaryocyte	1.4	1.2	1.0	1.4	1.2	1.4	1.4	1.0	0.4	0.6	1.0	0.8

TABLE 3.—*Marrow Cells in 35 to 120-Day-Old Ducks*

	Experimental Days									
	35	40	45	50	55	60	65	70	80	90
	Number of Ducks in Each Experiment									
	2	2	2	2	2	2	2	2	2	4
Proerythroblast	1.6	1.0	1.6	1.6	1.0	0.8	1.0	0.8	0.8	0.6
Erythroblast	7.7	7.9	7.4	7.0	8.5	8.4	8.2	8.0	8.1	8.0
Polychromatic erythroblast	30.4	32.2	30.0	29.6	27.7	29.4	26.0	26.2	25.3	24.0
Myeloblast	0.4	0.6	0.4	0.4	0.6	0.4	0.2	0.2	0.2	0.3
Eosinophile myelocyte	0.2	1.0	0.8	0.6	0.6	0.4	0.2	0.4	0.4	0.5
Eosinophile metamyelocyte	1.2	1.8	2.2	1.6	1.6	1.2	0.8	1.0	1.4	1.4
Eosinophile, band	1.4	1.2	1.2	0.8	1.0	1.2	1.0	0.8	0.8	1.1
Eosinophile, segmented	3.0	1.8	2.4	2.0	1.8	2.0	1.8	1.6	2.0	2.3
Heterophile myelocyte	0.6	4.0	3.4	3.8	3.0	2.8	2.4	2.6	2.3	2.8
Heterophile metamyelocyte	13.2	13.0	12.2	13.0	14.0	13.0	14.8	14.4	14.0	14.7
Heterophile, band	14.8	12.0	14.0	13.8	13.6	12.0	11.6	12.0	11.8	12.0
Heterophile, segmented	24.0	19.3	21.4	22.0	23.2	25.4	26.0	26.4	26.0	25.5
Lymphocyte	0.4	1.2	1.0	1.2	1.4	2.0	2.8	2.0	3.0	2.8
Monocyte	0.2	0.8	0.8	0.8	0.6	0.8	1.2	0.8	1.0	1.1
Plasma cell	0.4	1.4	1.2	1.6	1.0	1.4	1.8	1.8	1.4	1.8
Megakaryocyte	0.4	0.8	1.0	1.2	0.8	0.8	0.8	1.0	1.3	1.1

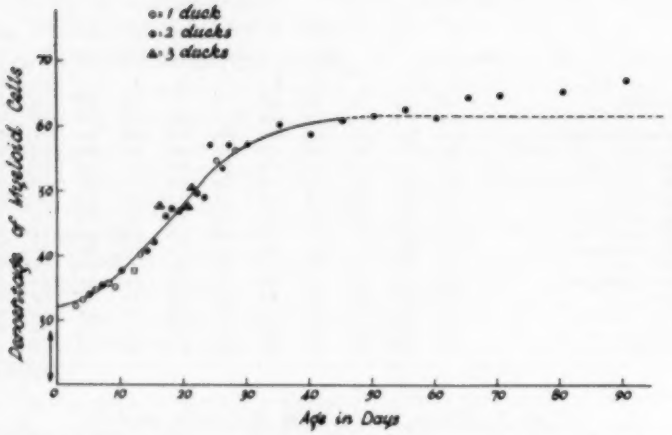

Fig. 2.—Erythroid cells predominate in the bone marrow of young ducks. They show a gradual decrease with increasing age of the duck. The erythroid-myeloid ratio is equal for approximately 10 days, then levels off to reach a plateau at approximately 2 months of age.

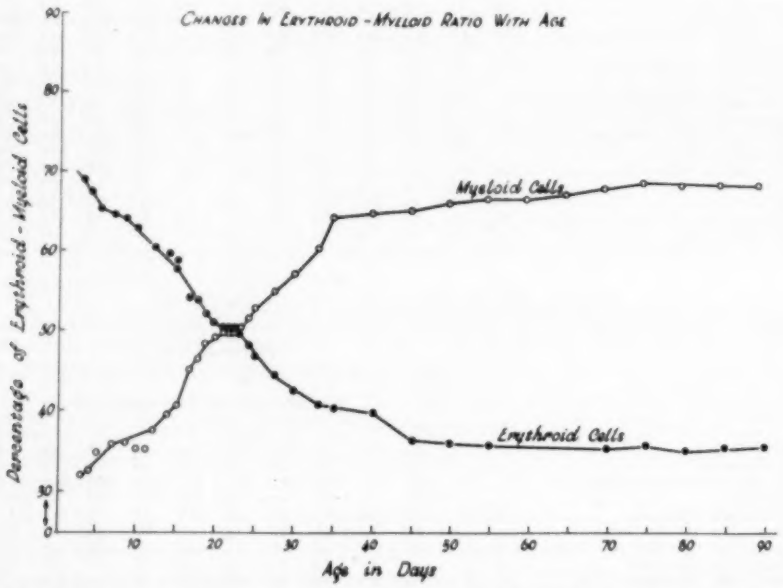

Fig. 3.—The data in Tables 1, 2, and 3 have been plotted in graphic form and are shown to fit a logistic curve. The latter part of the curve rises above the asymptote.

It is interesting to note in Figure 2 the marked preponderance of the erythroid elements in the very young duck and the rapidity with which this ratio changes. This erythroid-myeloid proportion is approximately equal in ducks 16 to 26 days of age. By the end of the fourth week the myeloid elements predominate. The myeloid series in the adult duck almost reversed the picture of that found in the very young birds, although it never quite reached the 2:1 ratio (Fig. 2).

The data have been plotted in terms of the percentage of white cells against the age of the ducks (Fig. 3). No simple curve was found which would fit the entire series. Graphic methods were used to fit a logistic curve which has the following general formula:

$$Y - d = \frac{K}{1 + ce^{-bt}}$$

Where Y = the percentage of white cell elements
d = the lower asymptote
$K + d$ = the upper asymptote
t = time, or age in days of ducks

Estimating $K = 32$ and $d = 30$ resulted in a curve which provides a good fit through the first 50 or 60 days. The equation for this curve is as follows:

$$Y - 30 = \frac{32}{1 + e^{1.87150 - 0.15117\,t}}$$

The latter part of the series shows a tendency to rise beyond the upper asymptote of the curve, but no attempt was made to fit the curve to this latter portion. It is clear that no general conclusions can be drawn from the fact that this curve provides as good a fit as it does. It merely represents an attempt to provide a smooth curve approximating average values throughout the series. The points plotted represent average values for one, two, or three ducks. Consideration was given to the elements of variability included in the scatter of points about the curve. Since each determination was based on a single count of a single smear from a single position in each of four bones, a special study has been made to provide a statistical analysis of these elements of variability and will be reported subsequently.*

COMMENT

Studies on the normal duck have revealed a marrow which changes with advancing age. For a relatively short span of approximately five days, the erythroid elements predominate in a 2:1 ratio. Within two weeks the erythroid and myeloid cells are in a 50-50 proportion. This equality of cells is maintained for another 10 days. By the end of the fourth week the number of myeloid cells begins slowly to increase. At the end of 70 days the duck reaches a plateau and a ratio of 1:1.8 in the myeloid-erythroid elements. This ratio is maintained throughout the period of this study, which included birds 90 days of age. Thus, the adult duck almost completely reverses the marrow picture from that which is present during the first week of life. Similar proportions of the cells in the bone marrow of chick embryos and chicks 7 days of age have been observed.[6]

* Statistical analysis was made by Dr. J. Allen Scott, Professor of Epidemiology and Medical Statistics of the University of Texas, and Mary Westbrook, graduate assistant.

These data show that in any experiment concerning blood variations in ducks the age must be carefully noted and all comparisons must be made on ducks of specific ages. Since the marrow of ducks before the age of 30 days is more active than that in later life, younger birds should provide better material for hematological experiments than older ones. All hematological studies on the bone marrow of ducks should be carefully controlled for each experiment.

In the morphological study of the myeloid cells of the duck, three separate and distinct forms of granulocytes are found in duck marrow. These types of granular cells are considered by us to be eosinophiles, basophiles, and heterophiles.

A similar classification of granulocytes in birds was given by Cook and Dearstyne,[7] although the granules in their description differ from those observed in the duck. Forkner [5] referred to these granulocytes of birds as "eosinophiles with rods and pseudo-eosinophiles." Magath [1] designated the polymorphonuclears in ducks as "leucocytes with eosinophilic granules and leucocytes with eosinophilic rods." Hewitt [2] used the terminology of "heterophils with ellipsoidal granules, and heterophils with bacillary granules." Obviously, much confusion has arisen in classifying these cells in the peripheral blood. A much better understanding of the different granular cells is obtained when marrow preparations are studied and the cells are traced to their precursors.

There exists in normal duck marrow two types of myelocytes. One has a pale blue cytoplasm filled with brilliant orange and orange-pink highly refractile granules resembling the eosinophilic myelocyte of mammalian marrow, and it is so designated in this paper. The other type of myelocyte has a blue cytoplasm with areas of pink, and contains two colors of granules, dark purple and dull yellow-orange. Because of the presence of multiple colors of granules, these cells all are tabulated as heterophile myelocytes in this paper.

From the myelocyte, cells can be traced to the metamyelocyte, to the heterophile band cell, and to the segmented forms. As the myeloid cell matures, the reddish-purple granules disappear and the dull orange-colored granules persist. A slow metamorphosis occurs in both the shape and the color of the orange granules. The myelocyte contains only round granules; the metamyelocyte has both round and ovoid granules, and the band heterophile cells show ovoid and elliptical granules. The mature heterophile has predominately elliptical granules.

SUMMARY

The differential cell count on the bone marrow of 50 normal ducks, from 3 to 90 days of age, is given.

The marrow varies with the age of the duck; there is almost a complete reversal in the erythroid-myeloid ratio in the young as compared with the older duck.

The granulocytes are classified as heterophiles, basophiles, and eosinophiles on the basis of their staining reaction and the shape of the granules.

These types of cells can each be traced to their separate myelocyte precursor.

The granules of the heterophile and eosinophile change their shape from round to oval to elliptical during the process of maturation. This change is not observed in the basophile series.

Absolute attention to techniques in obtaining, fixing, and staining of bone marrow is essential for good differentiation of cells in the duck's bone marrow.

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HISTOLOGIC STUDY OF INTRAPULMONARY VESSELS IN TUBERCULOSIS

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DESPITE much gross and microscopic study of tuberculous lesions in the lung, up to the present time relatively little specific work has been reported on histologic changes of the blood vessels in relation to such lesions. For this reason, a study was undertaken to observe and compare alterations occurring in vessels located in pulmonary tuberculous lesions, in regions adjacent to such lesions, and in uninvolved portions of the same lungs.

GENERAL BACKGROUND

In 1882, Weigert [1] concluded from his studies that miliary tuberculous lesions arose from the erosion of a tuberculous focus into the wall of a vessel, destroying its intima. He was able to demonstrate this occurrence in 50 to 70% of cases of miliary tuberculosis. Wilson [2] found bacillemia present in 25% of cases of early miliary tuberculosis and in 40 to 100% of cases of late disease. In 1901, Ohlmacher [3] was of the opinion that the endothelial elements of vessels in tuberculous lesions are stimulated into productive activity. As the process advances, the vessels are occluded from endothelial inflammatory reaction or thrombosis. He considered that this plugging of the vessels constituted one of the factors leading to necrosis and caseation of tuberculous foci.

Not long after, Klebs [4] wrote that not only are new vessels not formed in tubercles but the preexisting vessels at the site of developing tubercles undergo obliteration. He described fibrous narrowing and occlusion of many vessels in foci of chronic pulmonary tuberculosis.

From 1910 to the present time, although a great many studies have been made of pulmonary tuberculous lesions in general, few have included specific observations on small blood vessels. Brenner,[5] in 1935, made a study in six cases, in each of which tuberculosis involved pulmonary vessels. He observed that arteries and veins of all sizes were affected but that involvement of small vessels occurred most com-

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Abridgment of thesis submitted by Dr. Van Vleet to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

monly. He described an elastic artery with a diameter of 2.2 mm. in which the intima was normal but the media was completely necrotic. The adventitia showed rather inactive tuberculosis with much fibrosis, some caseation, and calcification continuous with a fibrocaseous patch in the adjacent pulmonary parenchyma. He noted involvement of several small veins in the region. He found involvement of small muscular arteries in five cases and observed the commonest lesion to be obstructive endarteritis. In no case were the changes sufficiently widespread to cause significant obstruction to the general pulmonary blood flow. Small veins were involved in three cases. He described thickening of the intima by loose fibrillar connective tissue containing many lymphocytes, polymorphonuclear leucocytes, and a few capillary lumina. Usually a similar process was seen in the media and adventitia, the whole wall then consisting of loose, cellular, vascular connective tissue. In some regions he observed a portion of the wall adjacent to a focus in the lung to be caseous. He noted involvement of large veins in only one case. More recent studies corroborate most of these findings; reference to such work will be made later.

MATERIALS AND METHODS

From the files of the Section of Pathologic Anatomy of the Mayo Clinic, 10 cases of active pulmonary tuberculosis were selected for study. The cases chosen were those in which there was no evidence of coexisting pulmonary disease, such as emphysema, or of cardiac disease, which in themselves might account for pathologic changes in the pulmonary vessels. To eliminate cardiac disease, no patients who had systemic hypertension, significant coronary arterial disease, or valvular disease were included in the study. The condition of the right ventricular wall was not taken by itself as a basis for either inclusion or exclusion of cases from the study, but it developed that in each of the cases employed the right ventricular wall was of normal thickness.

Two of the patients were male, and eight were female. The ages ranged from 2 to 50 years. The known duration of illness varied from 2 weeks to 20 years. While physiologic studies of pulmonary pressures had not been done in these patients, the fact that the right ventricular wall was not hypertrophied suggests that the pulmonary arterial pressure had not been increased in any of these patients. None of the patients had received any form of collapse therapy. Tubercle bacilli had been recovered on culture in all instances during life.

Blocks of tissue for section were taken from the lesion, from a region immediately adjacent to the lesion, and from an uninvolved region remote from the lesion in the same or the opposite lung. The blocks of tissue were embedded in paraffin; sections were stained with hematoxylin and eosin and with Verhoeff's elastic tissue stain, counterstained with Van Gieson's stain for connective tissue.

OBSERVATIONS

In general the changes in the arteries and veins within the lesion included acute inflammation, early and late phases of thrombosis, young granulomas, and healing granulomas. In tissue immediately adjacent to the lesion, the changes were of proliferative character. In uninvolved portions of lung, such changes were absent or else there was minimal increase in fibrous tissue in the walls of vessels.

Within the lesion, the earliest change observed in the arteries was infiltration by polymorphonuclear leucocytes and lymphocytes, usually associated with a slight increase in fibrous tissue and often associated with thrombosis (Fig. 1*a*). Small muscular arteries were seen with recent thrombosis and with organizing thrombi of varying ages. In some of these thrombosed arteries, young granulation tissue was seen involving all layers of the arterial wall (Fig. 1*b*). Other muscular arteries were seen in which the lumina were partially or completely occluded by connective

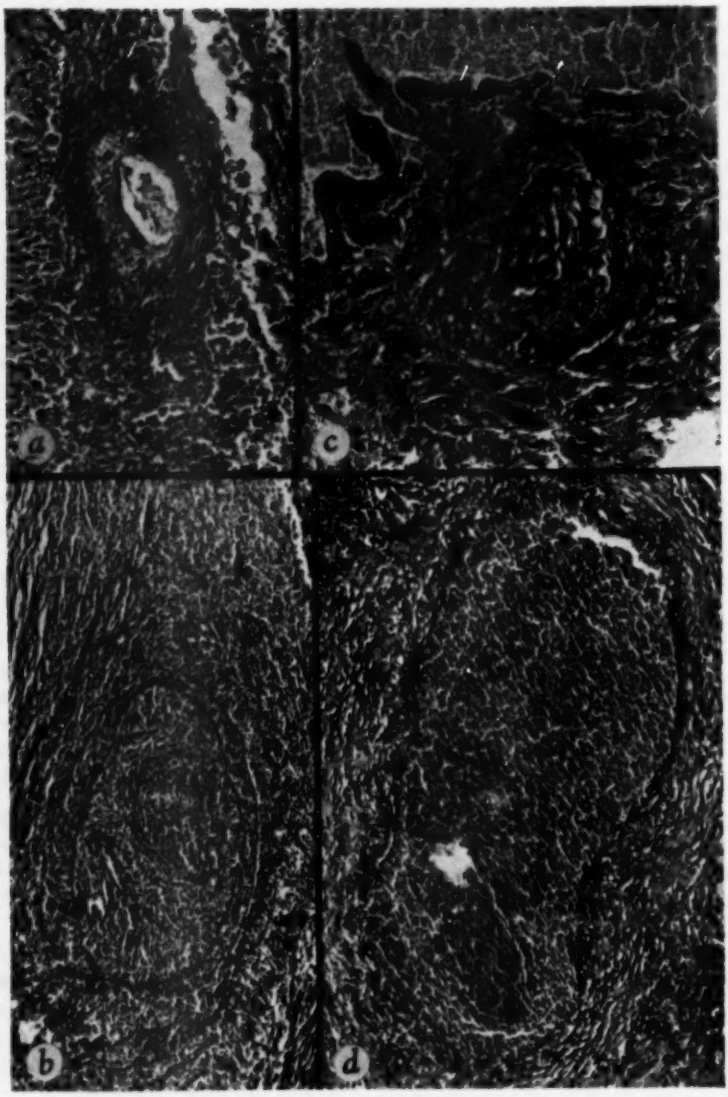

Fig. 1.—Small pulmonary vessels within tuberculous lesions. (*a*) Muscular artery showing leucocytic infiltration of wall, with fibrous intimal thickening causing luminal narrowing (ELVG;* × 150). (*b*) Muscular artery showing granulation tissue in all layers of wall (ELVG; × 125). (*c*) Muscular artery showing fibrous obliteration of lumen and scarring of wall (ELVG; × 125). (*d*) Vein, with wall involved by tuberculous granuloma and showing caseous necrosis. A recent thrombus is in lumen (hematoxylin and eosin; × 75).

* ELVG, used in this and the other legends, denotes Verhoeff's elastic tissue stain, counterstained by Van Gieson's method.

tissue that in some instances was young and vascular and in others was older and denser (Fig. 1*c*). In some arteries destruction was so extensive that only barely recognizable fragments of wall were visible.

Similar changes were noted in the veins. Early phlebitis, associated with young thrombi and some leucocytic infiltration, was seen (Fig. 1*d*). In other small veins, small young tubercles were observed to be involving the wall and partially occluding

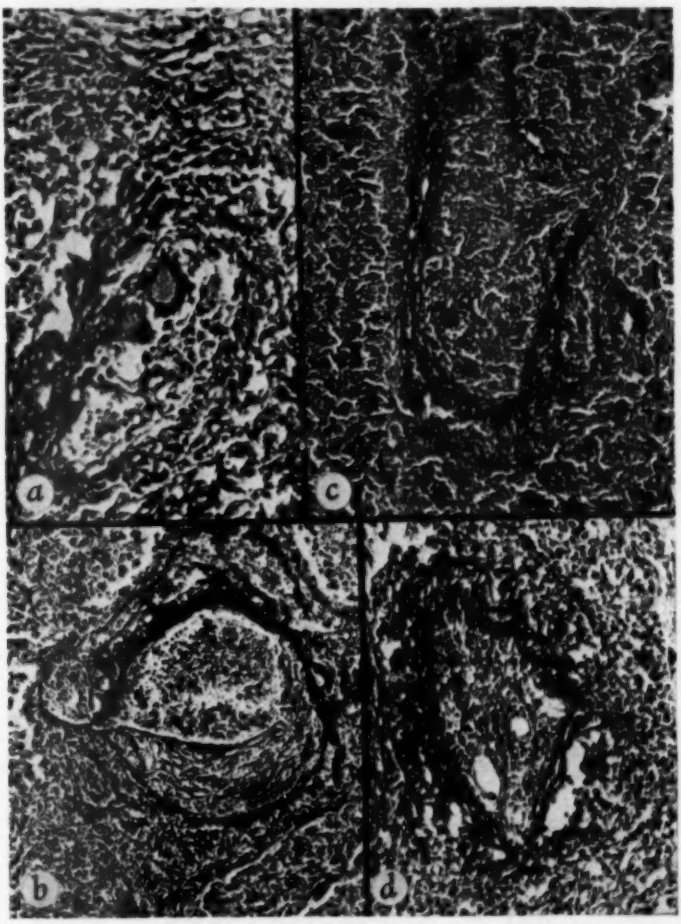

Fig. 2.—Small pulmonary veins in tuberculous granulomas. (*a*) Tuberculous phlebitis with giant cells (ELVG; × 200). (*b*) Narrowing of lumen by focal fibrous thickening of intima, with scarring of wall (ELVG; × 150). (*c*) Tuberculous phlebitis and thrombosis (ELVG; × 200). (*d*) Tuberculous granuloma of wall. A recanalized thrombus is in lumen (ELVG; × 150).

the lumina (Fig. 2*a*). Older lesions were also seen in which dense connective tissue narrowed the venous lumina to varying degrees; this resulted from either granulomatous lesions or organization of thrombi (Fig. 2*b*). Some veins showed even more

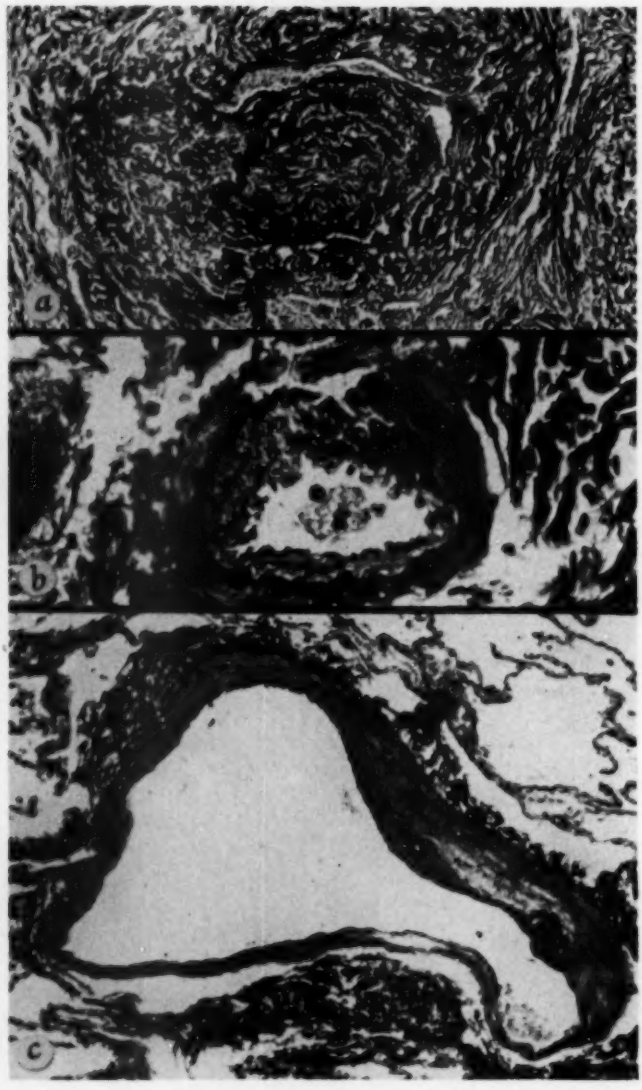

Fig. 3.—(*a*) Vein in tuberculous lesion showing scarring of wall and obliteration of lumen by fibrous tissue (ELVG; × 150). (*b*) Muscular artery at periphery of tuberculous lesion showing mild medial hypertrophy and moderate intimal fibrous thickening (ELVG; × 400). (*c*) Muscular artery at periphery of tuberculous lesion showing focal intimal fibrous thickening (ELVG; × 75).

entire wall or portions of the wall, leaving minimal remnants of its substance (Fig. 2*c*). Some of the thrombosed veins had become recanalized (Fig. 2*d*). In older lesions, the tubercles had been replaced by dense collagenous fibers that partially or completely occluded the lumina (Fig. 3*a*).

In the tissue immediately adjacent to each tuberculous focus studied, the changes observed in the vessels were chiefly proliferative in character and involved predominantly the intima (Fig. 3, *b* and c). These changes produced slight intimal narrowing. The veins in these regions also exhibited proliferative changes similar to those in the arteries.

In portions of lungs uninvolved by tuberculous lesions the vessels showed virtually no alteration from normal.

COMMENT

It is interesting to correlate and compare our observations with others that have been reported.

Davies [6] noted that the center of a tuberculous focus was avascular but that a zone of inflammatory reaction was present along the margin of a lesion. In the area of inflammation, the vessels were engorged and dilated, and periarteritis and endarteritis were present, with weakening of the wall of the vessel.

Goldberg [7] noted the presence of obliterating endarteritis in lesions of caseous pneumonia. In one case he noted a great reduction in the vascular bed with increased resistance to blood flow and hypertrophy of the right ventricle. In other cases, Goldberg noted obliteration of the vessels in pneumonic areas; he was of the opinion that this resulted from either edema of the wall and proliferation of the intima or caseous coagulation in the lumen of the vessel. He considered that the proliferative processes had occluded the arteries before they were exposed to the destructive action of tubercle bacilli.

Pinner [8] was of the opinion that the productive and obliterative angiitis, which he observed to develop rapidly in peripherally advancing margins of tuberculous foci, accounted for the fact that hemorrhages were not seen much more frequently. He noted the invasion of an artery by granulation tissue with formation of a thrombus and recanalization of the thrombotic mass. Similar examples were seen in the present study.

During a study of 18 cases of exogenous progressive pulmonary tuberculosis of the reinfection type, Terplan [9] noted the presence of striking tuberculosis periarteritis and endarteritis in a small branch of the pulmonary artery in tissue that was the site of caseating pneumonia. He also found distinct endarteritic lesions with fibrinoid necrosis in the wall and eccentric narrowing of the lumen in another case. In the latter instance, he noted lesions of obliterating endarteritis in small branches of the pulmonary artery in atelectatic portions of lung. He observed specific and inflammatory lesions of pulmonary arteries and veins in close topographic relation to progressive tuberculous processes but found no evidence that these lesions had become a source of hematogenous seeding. He noted obliterating endarteritis of smaller arterial branches in regions of considerable collapse and induration. As a result of his observations, Terplan was of the opinion that the concentric narrowing of the lumen caused by intimal proliferation was not necessarily of tuberculous origin but could be a reactive change of the wall of the vessel, conditioned by progressive collapse and induration with resultant permanent local strain on the pulmonary circulation.

A most interesting method of study was used by Charr and Savacool.[10] This consisted of removal of the heart-lung block at necropsy, injection of the pulmonary arteries with barium, and roentgenographic study of the preparation. Their observations revealed great individual variability of the vascular pattern in the areas surrounding tuberculous cavities. Extremely few vessels were visible in some foci, whereas a great abundance of vessels was noted in others. In general, they concluded that destruction of capillaries and arterioles and marked narrowing of the larger arteries were most prominent or definite in cases in which fibrous lesions had been present for more than five years. They found the arterioles to be completely occluded in pulmonary scars. Conversely, they found that arterial fibrotic lesions were not pronounced in cases in which the disease was of less than one year's duration and in which pulmonary scarring was minimal.

One of the more recent studies is that of Denst and associates,[11] who studied resected tuberculous lungs. Of the patients included in their study, 73 had undergone collapse therapy and 12 had not. They observed that the smaller arteries were more extensively and severely diseased than the larger. They also noted that porous, spongy granulation tissue occluded some of the arteries and that canalization by small endothelial channels occurred. They observed scarring and distortion of the media and adventitia with subsequent blending with adjacent granulation and fibrous tissue. In the parenchyma in collapsed areas, the vessels showed moderate intimal fibrosis, although they were otherwise normal. Minute arteriolar and precapillary changes were often widespread in collapsed but otherwise normal parenchyma remote from the tuberculous foci. Among their 12 patients who did not have collapse therapy, 4 had arterial lesions of moderate degree in regions remote from the tuberculous foci; 3 showed arteriolar lesions of moderate degree in such tissue. In none of these patients was the degree of change severe.

In general, the findings in our cases corroborated the findings of others in that all phases of involvement, from recent inflammatory reactions to scarred residues, were seen in both arteries and veins in tuberculous foci. The changes were most marked in the small arteries and veins within tuberculous lesions. Minimal changes occurred in tissue just outside the lesions, and no significant changes were seen in vessels remote from the tuberculous foci.

In none of our cases was there structural evidence, as judged by the size of the major pulmonary arteries and of the right ventricle, that pulmonary hypertension had existed. Assuming that pulmonary hypertension had been absent in these cases, this absence is explained by the fact that significantly narrowed vessels were found only in the tuberculous lesions. Thus, the majority of the vessels of the lungs were not involved by occlusive changes.

SUMMARY

Histologic changes of the blood vessels in involved and uninvolved portions of lung in cases of pulmonary tuberculosis were studied. Microscopic sections were made in 10 cases of active pulmonary tuberculosis from the tuberculous lesions, from tissue immediately adjacent to the lesions, and from grossly normal lung remote from the lesions.

Within the lesions, alterations in the vessels were seen frequently, and they varied in degree and age. These changes included recent arteritis and phlebitis,

recent and organized thrombi, and involvement of the wall with recent and old tuberculomas, producing destruction of the wall and leaving barely recognizable fragments.

In tissue immediately adjacent to the lesions, the changes observed were chiefly proliferative in character, involving mainly the intima and causing only minimal degrees of luminal narrowing.

In the sections of uninvolved lung remote from the lesions no significant alterations were noted.

In none of the cases studied was there any significant increase in right ventricular thickness or cardiac weight.

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TETRALOGY OF FALLOT: SURVIVAL TO SEVENTIETH YEAR

Report of a Case

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SURVIVAL beyond the third decade is unusual among patients with the tetralogy of Fallot.[1] Much less common is survival to the sixth decade,[2] and to my knowledge no case of survival until the latter part of the seventh decade has been previously recorded. For this reason the case of a man surviving to his 70th year is reported. This patient, who also had adenocarcinoma of the prostate gland with widespread bony metastases, died from a cerebral vascular accident.

REPORT OF CASE

E. B. (UH108436), a 67-year-old white man, entered the University Hospital March 11, 1952, complaining of severe low back pain and loss of 14 lb. (6.4 kg.) since mid-December, 1951. On the basis of rectal examination and roentgenograms showing osteoplastic secondary deposits in several ribs and vertebral bodies, a diagnosis of carcinoma of the prostate gland was made and treatment with diethylstilbestrol begun. This diagnosis was supported on March 19, when biopsy of an enlarged inguinal lymph node showed it to be largely replaced by adenocarcinoma.

For as long as he could remember the patient had suffered from easy fatigability, weakness, and exertional dyspnea. Recurrent bluing of the fingernails had been noticed for many years. A diagnosis of "congenital heart disease" was said to have been made when the patient was one year of age. A sister described him as having been "difficult to raise" on account of attacks of dyspnea and cyanosis associated with exertion. The patient nevertheless described himself as having been "quite a runner" in his early twenties, and he had apparently been able to work continuously until incapacitated by back pain in December, 1951. Mild swelling of the ankles had been present since early in 1951.

Physical examination disclosed slight cyanosis of the face and fingernail beds, but no clubbing. There was moderate edema of the feet and ankles. Pulse 64, regular. Blood pressure 130/75. A Grade 3 systolic murmur was heard over the precardium. The character of the murmur was blowing at the apex, but it was loudest 1 in. (2.5 cm.) from the sternal border in the fourth left intercostal space. The murmur was transmitted up the left side of the sternum and to the left axilla. The red blood cell count was 4,200,000 per cubic millimeter and the hemoglobin 13.3 gm. per 100 cc. Urinalysis revealed a faint trace of protein. Digitalis and diuretic therapy was instituted. The patient was discharged from the hospital March 29, 1952, to continue receiving digitalis, diuretics, and diethylstilbestrol at home.

He was readmitted June 19 in an agitated and depressed state after an impulsive attempt at suicide. After receiving five electroshock treatments he was discharged from the hospital June 30, his mental state much improved.

Jan. 11, 1953, the patient returned to the hospital by ambulance in a state of severe congestive heart failure. He had apparently stopped taking digitalis and diuretics at home and had been suffering from nocturnal asthma for the last 10 nights. The pulse was 120 a minute with occasional extrasystoles. The neck veins were engorged. There was marked edema of the ankles and lower legs, the liver was palpable, and there were signs of pulmonary edema. An electrocardiogram showed right axis deviation, sinus tachycardia, and ventricular extrasystoles. Digitalis and diuretic therapy was again instituted, and the patient was discharged Jan. 28 much improved.

From the Department of Pathology, University of Alberta.

The next admission was Sept. 26 for abscesses of the thighs resulting from self-administered injections of diuretic. This condition was treated successfully and the patient discharged Oct. 31. During this period in the hospital the fingernails were somewhat dusky in appearance, and the patient was mildly dyspneic but in no distress on this account. There was no edema of the feet or ankles. Pulse 72, regular. Blood pressure 152/82. Hemoglobin 14.6 gm. per 100 cc.

On Nov. 23 the patient entered the hospital in a wheel chair. He had been feeling weak, dizzy, and faint during the previous few days. He appeared pale and dusky, weak, and dyspneic. There was moderate edema of the ankles. Pulse 84, regular. Blood pressure 130/75. He became progressively confused and disoriented and complained intermittently of headache, but was able to be up walking around his room some days. Dec. 1 he developed flaccid paralysis of the right side of the face and the left arm. The left leg was hypertonic, and a Babinski response could be elicited. Death occurred Dec. 6 at the age of 69 years.

Autopsy Findings.—The heart weighed 450 gm. and showed right ventricular hypertrophy and dilatation and blunting and broadening of the apex. The right atrium was moderately dilated and hypertrophied. There was evident displacement of the pulmonary artery to the left and of the aorta to the right. The aortic arch and the descending aorta were left-sided. The ductus

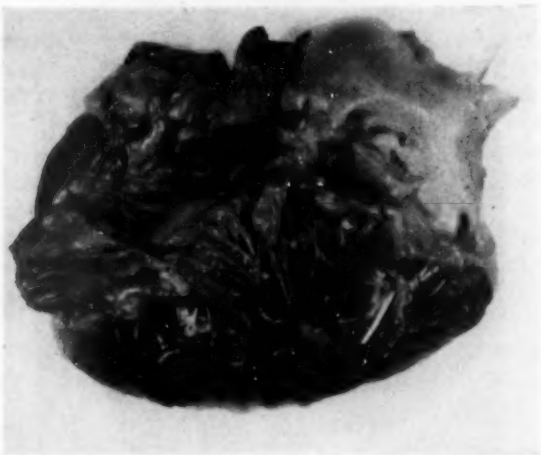

Fig. 1.—Main right ventricular cavity has been laid open by cut through its anterior wall parallel with septum. Aorta arises partly from right ventricle, overriding large ventricular septal defect. White marker enters orifice of infundibular stenosis and can be seen emerging from pulmonary artery at top right-hand side of photograph.

arteriosus was obliterated. The superior and inferior venae cavae entered the right atrium in the normal manner. Four pulmonary veins entered the left atrium by separate orifices. The foramen ovale was anatomically closed. Two coronary arteries arose from separate aortic sinuses of Valsalva. The vessel having the distribution of the right coronary artery arose from the anterior sinus, and that having the distribution of the left coronary artery arose from the left posterior sinus.

The aorta measured 2.5 cm. in diameter at a point 1 cm. above the aortic valve. The valve was tricuspid, with smooth pliable cusps, the orifice measuring 8 cm. in circumference. The aorta arose one-third from the right ventricle and two-thirds from the left ventricle, overriding a ventricular septal defect measuring 3 by 1.5 cm. The posterior portion of the right side of the saddle-shaped margin of this defect exhibited a sclerotic and calcified ridge 1.6 cm. long and 0.4 cm. wide (Fig. 1). The hypertrophied crista supraventricularis extended downward, forward, and to the right from the margin of the ventricular septal defect to join the right ventricular wall. In so doing, this "false septum" separated the outflow or infundibular portion from the main right ventricular cavity, creating the so-called "third ventricle" (Fig. 2). This false

chamber communicated with the main right ventricular cavity through a foramen 1.0 by 0.3 cm., which was obviously a space between two trabecular muscles. The margins of this orifice were irregular, hard, and sclerotic, with considerable calcification. The infundibular chamber measured 2.7 cm. long, 3.5 cm. wide, and 0.7 cm. deep. The pulmonic valve was located 1.5 cm. above the upper margin of the infundibular stenosis and was bicuspid, the two cusps being soft, pliable, and of equal size (Fig. 2). There was no pulmonic valvular stenosis, the circumference of the orifice being 8 cm. The pulmonary artery was not dilated, having a diameter of 2.7 cm. at a point 1 cm. above the valve. The myocardium of the right ventricle was hypertrophied, with large papillary muscles. The thickness of the right ventricular wall near the septum as measured 2 cm. below the atrioventricular sulcus was 1.0 cm. The thickness of the corresponding portion of the wall of the left ventricle was 1.2 cm. The tricuspid orifice measured 10 cm. in circumference. The valve displayed three normally disposed leaflets with considerable calcification at their bases. The calcified base of the anterior tricuspid leaflet joined the stone-like ridge on the margin of the septal defect. The mitral orifice, measuring 9 cm. in circumference, was guarded by two normally disposed, soft, smooth leaflets.

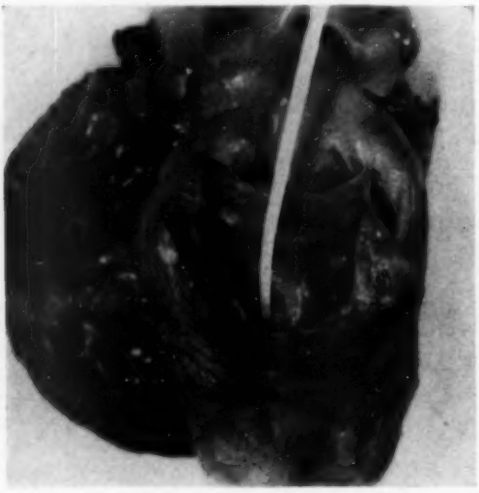

Fig. 2.—Pulmonary artery and infundibular chamber have been opened by vertical cut through their anterior walls. Pulmonic valve is bicuspid. White marker enters infundibular chamber through its stenotic orifice, passing through valve and up pulmonary artery.

Other autopsy findings confirmed the diagnosis of adenocarcinoma of the prostate gland with widespread osteoplastic bony metastases. In addition, the major portion of the left cerebral hemisphere showed encephalomalacia. No occlusion was demonstrated in the intracranial portions of the internal carotid arteries or in the circle of Willis and its branches. The common carotid arteries were atherosclerotic. The condition of the cervical portions of the internal carotid arteries is not recorded in the autopsy protocol.

COMMENT

This case of tetralogy of Fallot is remarkable for prolonged survival, the patient dying at 69 years of age from a cerebral vascular accident. The average period of survival in Abbott's series was 12 years.[1] The degree of overriding of the aorta has been mentioned as a factor of importance in regard to functional efficiency.[3] In the case presented only one-third of the aortic diameter overrode the right ventricle. Moreover, the channel leading from the right ventricle into the aorta

was reduced in size by a hard, irregular, calcified ridge projecting from the right side of the lower margin of the septal defect. In spite of the degree to which this shelf-like structure may have compensated for the overriding of the aorta, the comparatively good cardiorespiratory function in this patient was striking in view of the marked degree of infundibular stenosis present. The thesis of Bing and associates,[4] who demonstrated an excess of pulmonary capillary blood flow over pulmonary artery blood flow in older patients with the tetralogy of Fallot, may find application in this case, but unfortunately such studies were not carried out, nor were the bronchial arteries demonstrated at autopsy. Unlike Miller's case,[2] with survival to the 57th year, our patient had no pleural adhesions which, when vascularized, might have augmented bronchopulmonary anastomosis.

Bicuspid pulmonic valve is a frequent finding in the tetralogy of Fallot. Three of 11 cases showing infundibular stenosis without valvular stenosis in the series of Brinton and Campbell[3] had bicuspid pulmonic valves. One is tempted to invoke the theory of Spitzer[5] to explain such cases of tetralogy, even though it lacks confirmation in studies of mammalian embryology. On the other hand, in the case presented, no congenital ridge was found in the sinus of either pulmonic cusp, as described in certain cases by Koletsky.[6] There was, however, a small fibrous band in the bottom of the sinus of each of the two cusps. Whether eccentricity of the truncus-conus ridges was responsible for the occurrence of the bicuspid pulmonic valve[7] in this case seems questionable in view of the normal diameters of the aorta and pulmonary artery.

The formation of the so-called "third ventricle" has been described by Edwards and associates[7] as due to displacement of the crista supraventricularis by the dextroplaced aorta. Somewhat similar observations were made by Harris and Farber.[5]

Cerebral vascular accident, to which death is attributed in this case, is frequent in the tetralogy of Fallot, judging from Abbott's series.[1]

SUMMARY

A case of the tetralogy of Fallot with survival to the end of the seventh decade is reported. Death was due to massive encephalomalacia of the left cerebral hemisphere. The patient also had adenocarcinoma of the prostate gland with widespread osteoplastic bony metastases.

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6. Koletsky, S.: Congenital Bicuspid Pulmonary Valves, Arch. Path. **31**:338-353, 1941.

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News and Comment

Laboratory Refresher Training Courses.—The following schedule of Laboratory Refresher Training Courses is offered by the Communicable Disease Center during the period July, 1954, through June, 1955. Information and application forms should be requested from Laboratory Training Services, Communicable Disease Center, United States Public Health Service, P. O. Box 185, Chamblee, Ga.

Laboratory Diagnosis of Bacterial Diseases
8.40...Part 1. General Bacteriology
Sept. 13-24, 1954

8.41...Part 2. General Bacteriology
Sept. 27-Oct. 8, 1954

Laboratory Diagnosis of Parasitic Diseases
8.00...Part 1. Intestinal Parasites
Sept. 13-Oct. 8, 1954
8.01...Part 2. Blood Parasites
Oct. 11-29, 1954

Laboratory Diagnosis of Rabies
8.26...Oct. 18-22, 1954

Laboratory Diagnosis of Viral and Rickettsial Diseases
8.20...Oct. 18-29, 1954

Laboratory Diagnosis of Bacterial Diseases
8.50...Enteric Bacteriology
Oct. 18-29, 1954

Laboratory Methods in Medical Mycology
8.15...Part 1. Cutaneous Pathogenic Fungi
Nov. 1-12, 1954
8.16...Part 2. Subcutaneous and Systemic Fungi
Nov. 15-26, 1954

Laboratory Diagnosis of Tuberculosis
8.55...Nov. 15-26, 1954

Laboratory Methods in the Study of Pulmonary Mycoses
8.17...Nov. 29-Dec. 10, 1954

Laboratory Diagnostic Methods in Veterinary Mycology
9.40...Dec. 13-17, 1954

Laboratory Diagnosis of Rabies
8.26...March 14-18, 1955

Laboratory Diagnosis of Viral and Rickettsial Diseases
8.20...March 14-25, 1955

Laboratory Diagnosis of Malaria
8.05...Presented by special arrangement

Virus Isolation and Identification Techniques
8.21...Presented by special arrangement

Laboratory Diagnosis of Influenza
8.25...Presented by special arrangement

Typing of Corynebacterium Diphtheriae
8.42...Presented by special arrangement

Special Problems in Enteric Bacteriology
8.51...Presented by special arrangement

Phage Typing of Salmonella Typhosa
8.52...Presented by special arrangement

Courses 8.26, 8.20, 8.21, and 8.25 will be presented at the Virus and Rickettsia Laboratories, Montgomery, Ala. Other courses listed will be presented at the laboratories at Chamblee, Ga.

Completion of course 8.15, or equivalent education or experience, is a prerequisite for course 8.16.

The roster of course 8.20 will close 6 weeks prior to the beginning of the course.

Awards.—Dr. Sidney Farber, Professor of Pathology, Boston Children's Hospital, Harvard Medical School, was recently honored by receiving one of four awards given in recognition of achievements in cancer research. These awards, in memory of Katherine Berkan Judd, are administered by the Sloan-Kettering Division of Cornell University Medical College.

Awards.—Of the four Lederle Medical Faculty Awards given this year, three went to pathologists; namely, Dr. Fred V. Lucas, Department of Pathology, University of Rochester; Dr. George E. Murphy, Department of Pathology, Cornell University Medical College, and Dr. James Robert Teabeaut II, Department of Pathology, University of Tennessee. These awards are given to strengthen preclinical departments of medical schools in the United States and Canada.

Awards.—Dr. Jean R. Oliver, Distinguished Service Professor, State University of New York College of Medicine, has been given a Borden Award of a gold medal and $1,000, in recognition of his studies in the field of renal pathology.

Applications for Grants in Cancer Research.—Acting for the American Cancer Society, the Committee on Growth of the National Research Council is accepting applications for grants-in-aid for cancer research in the United States. Applications received before Oct. 1 will be considered during the winter, and grants recommended at that time become effective on July 1, 1955. Investigators now receiving support will be notified individually regarding their application for renewal.

The Committee feels that an understanding of cancer depends upon a deeper insight into the nature of the growth process, normal and malignant. Therefore, the scope of the research program is broad and includes, in addition to clinical investigations on cancer, fundamental studies in the fields of cellular physiology, morphogenesis, genetics, virology, biochemistry, metabolism, nutrition, cytochemistry, physics, radiobiology, chemotherapy, endocrinology, and environmental cancer.

Application blanks and additional information may be obtained from the Executive Secretary, Committee on Growth, National Research Council, 2101 Constitution Ave, N.W., Washington 25, D. C.

Meetings.—The Cascade County Medical Society will sponsor its fifth annual Medical Surgical Conference at the Meadow Lark Country Club, Great Falls, Mont., June 14-15. Chairman of the program committee of the conference is Dr. John A. Layne, Great Falls.

The Montana Obstetrical and Gynecological Society at its annual meeting in Billings, Mont., elected Dr. Harold W. Fuller, Great Falls, Mont., president.

Inter-Society Cytology Council Meeting.—The second annual meeting of the Inter-Society Cytology Council will be held in Boston, Friday and Saturday, Nov. 12 and 13, 1954. Those having material to present are invited to submit three copies of the title and an informative abstract of not more than 200 words to Dr. John B. Graham, Chairman of the Program Committee, 32 Fruit Street, Boston, before July 15, 1954. Abstracts of all papers accepted will be published in the official program.

Papers will limited to fifteen minutes. They will be discussed in related groups rather than individually. A maximum of eight papers will be presented at each session.

Particular attention is suggested for the endometrium and lesions of the gastrointestinal and urinary tract.

The authors of papers, selected for presentation, will be notified by Sept. 30, 1954.

The Scientific Program will comprise four consecutive sessions.

Section 1. Special Techniques; including Cytochemistry, and Ultraviolet and Electron Microscopy.....Chairman, Dr. James W. Reagan.

The second half of the section will be devoted to General Cytology.

Section 2. Prognosis in the Treatment of Cancer by Cytologic and Histologic Techniques.....Chairman, Dr. Arthur T. Hertig.

Section 3. New Developments in Cytology.....Chairman, Dr. Emerson Day.

Section 4. Round Table Discussion of the Carcinoma in Situ Lesion .....Chairman, Dr. John R. McDonald.

Place of Meeting, Statler Hotel, Boston. You are urged to make your reservations directly with the Reservations Manager, Statler Hotel, Boston.

Registration will be open to everyone interested in cytology. Registration fee for physicians is $5.00; for cytologic technologists, technicians, and others, $2.00. Medical students, interns, and residents will be admitted without charge.

An informal cocktail party and dinner will be held Friday night, Nov. 12. The annual business meeting will follow the luncheon at 12:30 Saturday, Nov. 13.

For additional information please contact the Secretary-Treasurer, Inter-Society Cytology Council, 634 North Grand Boulevard, St. Louis 3.

Books

Manual of Clinical Mycology. By Norman F. Conant, David T. Smith, Roger D. Baker, Jasper L. Callaway, and Donald S. Martin. Second Edition, Price, $6.50. Pp. 456, 202 figures. W. B. Saunders Company, 218 Washington Sq., Philadelphia 5, W. B. Saunders Company, Ltd., 7 Grape St., London W. C. 2, 1954.

Pathologists will welcome this second edition as they did the first. Eighty-eight new illustrations have been added and the references have been brought up to date. Two chapters have been added, one on the fundamentals of mycology, and the other on contaminants which may complicate the cultural diagnosis. New material is presented demonstrating the value of the periodic acid-Schiff stain for the demonstration of fungi in tissues, as well as recent information relating to histoplasmosis and other advances in mycology. The systematic treatment of each subject, briefly and clearly, together with the excellent photographs, makes this manual of value to all concerned with problems of mycotic disease.

The Biochemistry of the Nucleic Acids. By J. N. Davidson, D.Sc., M.D. (Edin.), F.R.I.C. Second Edition. Price, $2.25. Pp 200, with 15 figures. John Wiley & Sons, Inc., 440 4th Ave., New York 16, 1954.

This little book, of convenient pocket size, is intended, according to the author, "to provide an elementary outline of the main features of the nucleic acids and nucleoproteins for the benefit of students of biochemistry, of chemists who wish to know something about the biological aspects of the subject, and of biologists who wish to learn a little about the chemical aspects." In fifteen short chapters the author deals with such phases as histochemical tests for nucleic acids, the nucleic acid content of tissues, nucleic acids in the cell cytoplasm, the cell nucleus, and the metabolism, biosynthesis, and biological activity of the nucleic acids. Each chapter has a list of references to recent work. The reader will find in this book an interesting and compactly written account of the developments in this rapidly growing area.

Histopathology of the Skin. By Walter F. Lever, M.D. Second Edition. Price, $12.00. Pp. 518, with 281 illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1954.

The first edition of this volume, which appeared in 1949, has found widespread acceptance among pathologists and dermatologists. The many changes in the field of dermatopathology in the past few years necessitated revision of the original volume and have been incorporated in the present edition. The concise presentation and excellent photomicrographs which made the first edition so popular have been preserved. The material on vesicular and bullous lesions has been rewritten and correlated in a separate, new chapter. The chapter on nevi and melanomas has also been rewritten to recognize the wide acceptance of the histogenesis theory of the nevus cell proposed by Masson. New material on beryllium granuloma, papular myxedema, porphyria, ochronosis, and hemangiopericytoma has been included. The bibliographies of each of the chapters have been brought up to date. Many new photomicrographs have been added, including some excellent reproductions in color. All of these changes have served to improve a book that has already proved its value. It is to be anticipated that the present edition will be more useful and will find even greater popularity among those interested in diseases of the skin.

Die Bedeutung des Blutchemismus: Besonders in Beziehung zu Tumorbildung und Tumorabbau: Volume 2. Prof. Dr. Ernst Leupold, Price, $11.40. Pp. 207, with 102 illustrations. Georg Thieme, Diemershaldenstrasse 47, (14a) Stuttgart-O; agents for U. S. A.: Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1954.

This is the second volume of a monograph, the first part of which was published in 1945. The author has attempted an experimental investigation of how cellular and tissue metabolism is related to the causation of disease, in this instance to tumor formation and degradation. It is claimed that very small concentrations of metabolic materials that occur under physiological conditions will produce tumors and other diseases when parenterally administered. Upsetting the quantitative relationships of the cholesterol:sugar:phosphorus ratio in the blood will cause tumors to arise or be reduced in size. If true, the claims would open up new vistas in oncogenesis in rabbits. The data provided, however, are not convincing and confirmation is desirable.

Atlas of Exfoliative Cytology. By George N. Papanicolaou, M.D., Ph.D. Price, $18.00. Pp. 312, with 36 color plates. Published for The Commonwealth Fund by Harvard University Press, Cambridge 38, Mass., 1954.

The present work supplements and expands the previous volumes by Dr. Papanicolaou on cytologic studies of the female genital tract. The first portion of this large, loose-leaf book is composed of a discussion of the techniques of exfoliative cytology and the general criteria for the identification of malignant tumors by this method. Other chapters discuss, in turn, the application of cytology to the female genital system, the urinary and male genital systems, the respiratory system, the digestive system, exudates, and the breast. The second half of the atlas is made up of a series of 36 plates, in part drawings and in part photomicrographs, all in color, illustrating most of the cell types found in various smears. Here the sequence parallels the first half of the book, and each plate is accompanied by a short description of the various cells illustrated.

The need for a comprehensive volume on exfoliative cytology has become increasingly apparent with the rapid growth of this field in recent years. With the hope that such a volume would serve both as a manual for those studying cytologic diagnosis and as a basis for further study in this field, the Cornell group has asesmbled from their material of recent years the "Atlas of Exfoliative Cytology." Recognizing the rapidity of change in this field and the limitations of present knowledge, the author has adopted a loose-leaf format with the expectation of periodically adding appropriate material. Indeed, the author invites additions from other investigators in the field. The completeness of the present volume, as well as the provision for the addition of new material, makes this atlas a highly valuable aid to all persons studying exfoliated cells, whether on a diagnostic or investigative basis.

Lectures on the Thyroid. By J. H. Means. Price, $3.00. Pp. 113, with 11 illustrations. Harvard University Press, Cambridge, Mass., 1954.

This little book comprises five lectures given by Dr. Means at various times between June, 1949, and April, 1953. They are written in simple language, and each is accompanied by a list of selected references. The lectures represent thoughts of the author after more than forty years of interest in the thyroid gland. They are entitled

1. The Integrative Action of the Endocrine System
2. The Thyroid Hormone—Certain Aspects of Its Elaboration in the Body, the Significance of Its Structure, and of Its Action on End-Organs
3. The Use of Hormones, Drugs, and Radiations in the Management of Thyroid Diseases
4. Clues to the Etiology of Graves's Disease
5. The Need for Iodine

The book is dedicated to Dr. Means's colleagues of the Thyroid Clinic of the Massachusetts General Hospital. It will be of particular interest to medical students and to all physicians who desire a clearer idea of the problems of thyroid function and pathology, summarized by a master of his subject.

Klinische Zytologie: Grundriss der allgemeinen Zytologie und der Zytodiagnostik. By H. J. Streicher, Assisant, Chirurgischen Universitätsklinik, Heidelberg and St. Sandkühler; Assistant, Ludolf Krehl-Klinik, Heidelberg, with the assistance of Otto A. Roth, Assistant, Universitäts-Frauenklinik Tübingen, and W. Schwenkenbecher, Physician, Inneren Abteilung des Kreiskrankenhauses Sulingen/Hann. Price, dm 49.80. Pp. 196, with 58 predominantly colored illustrations. Georg Thieme, Diemershaldenstrasse 47, (14a) Stuttgart O (American Zone), 1953.

This is a well-written little book dealing with cellular details of normal structures and of various tumors. Also, the cytology of certain granulomas, such as tuberculosis, Boeck's sarcoid, and undulant fever, is discussed. Comparison of abnormal cells and those of normal tissues and structures is made continuously, for the benefit of those who are not familiar with the cytological appearance of various normal organs. A short historical review and an appendix of technical methods enhance the value of the book. Many of the discussions refer to smears taken from various lesions of organs after they have been removed from the patient to be used for study, and relatively few deal with smears taken for diagnostic purposes. Thus, while this book is an important guide for study of cellular details per se, it is not of great help to those who must look at smeared preparations for diagnosis of perhaps clinically unrecognized lesions. Nevertheless, this book fulfills a specific demand and can well be recommended. There are 58 excellent illustrations, many of which are in color.

A Manual of Tropical Medicine: By Thomas T. Mackie, George W. Hunter III, C. Brooke Worth, and 24 other collaborators. Second Edition. Price, $12.00. Pp. 907, with 304 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; W. B. Saunders Company, Ltd., 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1954.

This second edition brings up to date a wealth of practical information on all aspects of tropical medicine. The volume will undoubtedly be of value to many physicians who are in the armed forces or who are abroad for other reasons and who need a ready and abbreviated source of knowledge on the essentials of tropical disease. It may also be helpful to postgraduate physicians reviewing for board examinations and for medical students who wish to read a thumbnail sketch of the clinical aspects of parasitology.

In general, the pathological aspects of the multitude of diseases considered are briefly, but accurately, described and well illustrated. This book should also be of interest to many pathologists because of its emphasis on epidemiology, clinical-pathological correlation, and its excellent consideration of vectors and intermediate hosts. It contains new summaries of epidemic hemorrhagic fever, toxoplasmosis, trachoma, the virus encephalitides, rickettsialpox, trench fever, tropical nutritional diseases, effects of heat, etc.

We agree with the authors that it is most regrettable that a bibliography was not included. In a manual of this sort, which must of necessity be very brief on many important subjects, a brief but up to date bibliography would do much to increase its usefulness in civilian as well as military medicine. Surely, if the bibliography were printed in fine type it would not add enough to the size of the volume to be prohibitive.

Histopathologic Technic and Practical Histochemistry: By Dr. R. D. Lillie, Medical Director, United States Public Health Service; Chief, Pathologic Anatomy Service, Clinical Center, National Institutes of Health; and Chief, Laboratory of Pathology and Pharmacology, National Institute for Arthritis and Metabolic Diseases. Price, $7.50. Pp. 501, with 3 illustrations. Blakiston Company, 575 Madison Ave., New York 22, 1954.

This expanded treatise which was first published in 1947 under the title of "Histopathologic Technique" retains its practical approach to the various histological methods which are useful in the pathological laboratory. In this volume the author has added many of the newer histochemical methods which are proving to be of value to the practicing pathologist and the investigator.

Its logical organization, simple and definite directions, and its numerous references to original methods make it a valuable reference for the technician as well as the researcher. In many instances the inclusion of brief explanations of procedures, the summarizing of results which may be expected, and the frank admission of ignorance where the relative value of various methods are not known make the volume particularly helpful and reliable.

The enlargement of this edition has added to its cost. But it is probably well worth it to have within one cover such a comprehensive group of techniques subjected to the evaluation of one whose practical knowledge and experience and overall critical perspective can contribute so much.

Fundamentals of Neuropathology. By William Brooks Dublin. Price, $18.50. Pp. 496, with 329 illustrations and 3 colored plates. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1954.

The guiding principle of this most recent addition to the growing number of textbooks of neuropathology is stated in the preface as a conviction that neuropathology should be considered as general pathology extended to a consideration of the nervous system. This principle is followed throughout the text, with generally admirable results. The whole field of neuropathology is covered, but special attention is devoted to the more commonly encountered lesions and those systemic diseases which affect the nervous system. The author's background in general pathology makes for a felicitous handling of the material in these areas. The sections especially notable for their excellence are those on tumors and inflammations, the latter including a good survey of the connective tissue diseases. There is a refreshing lack of a prolonged discussion of the controversy over what constitutes inflammation in the nervous system. Instead, the reactions of the nervous system to toxins and organisms are treated in accordance with generally applicable principles and in the terminology of general pathology. Traditional neuropathological terms of approximate equivalence, however, are unfortunately not specified in the discussion of regressive neuronal changes. Appropriately, in a book of this kind, comparatively little space is devoted to rare and obscure entities such as the hereditary ataxias and the group of diffuse scleroses.

In this highly creditable attempt to bridge the gap between general pathology and neuropathology one misses, in places, the balancing influence of a clinical neurological background. For example, paralysis agitans is described in relation to von Economo's encephalitis with a good description of the corresponding inflammatory and degenerative changes in the substantia nigra and globus pallidus. The author then dismisses the other two most common forms of Parkinsonism by indicating simply that the syndrome may also be caused by arteriosclerosis, and that a sizable number of cases have no known cause. There is no discussion of the well-known and striking lacunar degeneration of the lenticular nucleus which so often forms the basis of the syndrome of arteriosclerotic rigidity, and no discussion of the purely parenchymatous changes in the degenerative form of Parkinsonism. Similarly, in the section on intervertebral disk lesions, the statement is made that "cervical lesions are infrequent," and the remainder of the discussion

is confined to degeneration of lumbar disks with nerve root compression, when actually degenerative disease of cervical disks with chronic trauma to, and circulatory embarrassment of the spinal cord is one of the leading causes of progressive spastic paraplegia in the adult.

On the whole, however, the author's purpose of contributing to a closer relation between general pathology and neuropathology has been well fulfilled. The book is profusely illustrated with beautifully reproduced and well-chosen gross and microscopic photographs.

Rudolf Virchow: Doctor, Statesman, Anthropologist. By Erwin H. Ackerknecht. Price, $5.00. Pp. 304. The University of Wisconsin Press, 811 State St., Madison 5, Wis., 1953.

It would be probably accepted without much contradiction that Rudolf Virchow ranks with the greatest in the history of medicine, and that nobody has surpassed him in stature in the history of pathology. Such general acceptance of his eminence is based on tradition, but rarely on familiarity with his true achievements.

It is truly gratifying that the distinguished medical historian of the University of Wisconsin has undertaken to give us a scholarly and well-documented history of this great personality. Already, the title gives an idea of the extent of Virchow's interests and contributions. He was truly a doctor, a statesman, and an anthropologist. That he is best known as a pathologist is partly due to his greater concentration in this area, but also due to our lack of familiarity with and interest in the other two fields.

The three phases of Virchow's activities are treated in three main parts of the book. The readers of this journal will enjoy the account of the development of Virchow's ideas on "cellular pathology," for which he is best known among us. The other chapters will astound most readers with the unbelievable spread of Virchow's interests, activities, and contributions. A few examples follow:

In 1848, Virchow simultaneously worked on blood and on cholera, wrote an extensive report on sanitary conditions in Upper Silesia, edited his famous contribution under the title of "The Medical Reform," and was extensively active in politics In the 1860's, he was simultaneously and actively engaged in widespread political activities, experimented with Trichinae, wrote his book on tumors, fought for improvement of sanitation, especially of sewage disposal in Berlin, started his archeological excavations, and did the routine work of a busy professor of pathology.

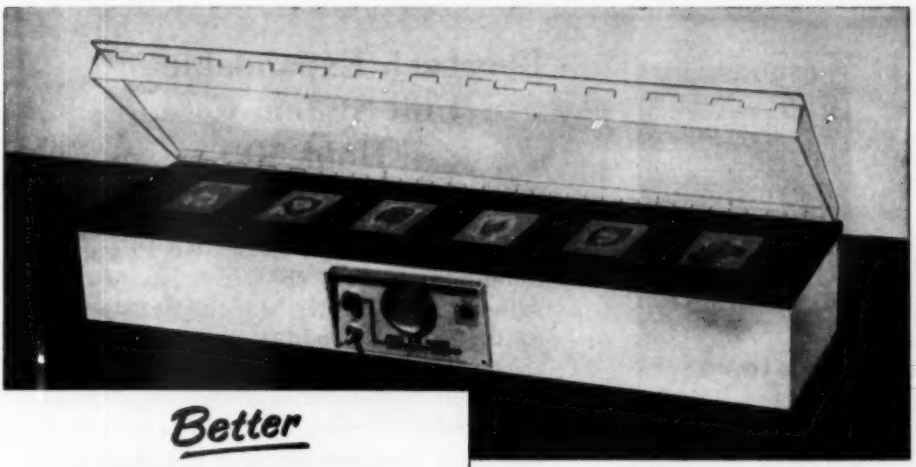
The presentation is clear and highly objective. Virchow, with all his greatness, was human and not without faults. These are realistically pointed out.

The book is recommended without reservation to historically minded physicians and pathologists. It will be an inspiration to all who read it.

Über hormonale und morphologische Malignität bei Nebennierengeschwülsten. By Friedrich Stein. Pp. 77, with 28 illustrations. Gustav Fischer, Villengang 2, Jena 15b, Germany, 1954.

Year Book of Pathology and Clinical Pathology (1953-1954 series). Edited by William B. Wartman, M.D. Price, $6.00. Pp. 485, with 174 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1954.

This volume is the first of this series under the editorship of William B. Wartman, and is divided, as in the past, into two sections: pathology and clinical pathology. Dr. Wartman has attempted to select articles "chiefly for their timeliness or the new concepts they describe or because they explore unknown areas in which it seems likely that important advances will be made in the future." In addition to the articles which have been selected for comment, taken from journals received from January, 1953, through December, 1953, there are four special articles: one by Thomas C. Laipply on Bronchiolar Tumors of the Lung, one by Douglas A. MacFadyen on Isotopes in Clinical Chemistry, one by Roger D. Baker on Diagnostic Methods Useful in Detecting Mycotic Infections, and one by Karl Singer on the Clinical Significance of Abnormal Human Hemoglobins. The book is printed on an excellent quality of paper. The illustrations are well-selected and well-printed. This year book should be of interest and value to pathologists and to others interested in the advances in this field. It maintains the high standards established in the earlier editions by Howard Karsner and Arthur H. Sanford.



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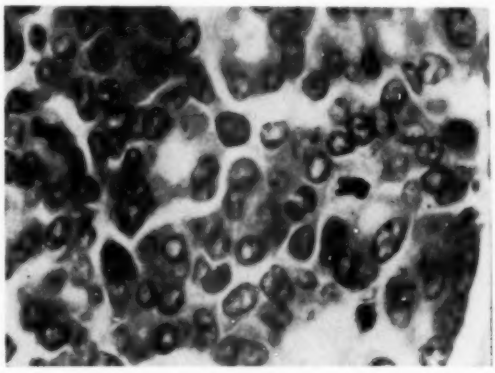

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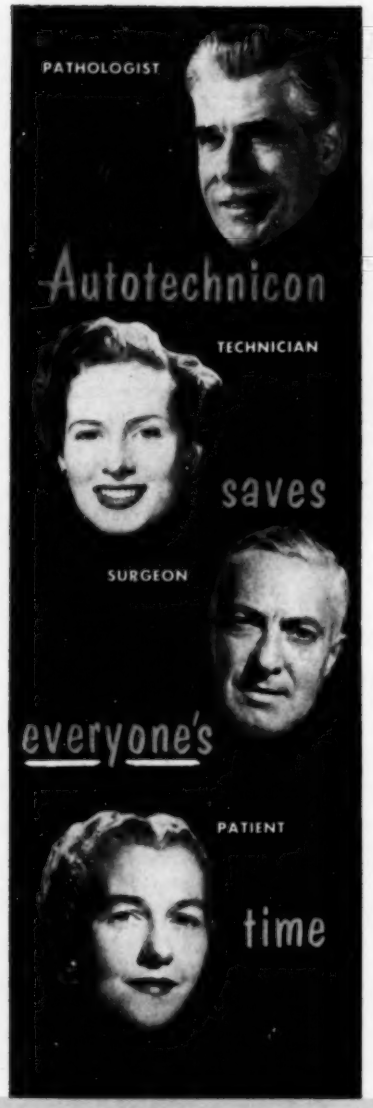

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